Guidelines on the use of extracorporeal photopheresis

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ORIGINAL ARTICLE

Guidelines on the use of extracorporeal photopheresis

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Abstract

Background After the first investigational study on the use of extracorporeal photopheresis for the treatment of cutaneous T-cell lymphoma was published in 1983 with its subsequent recognition by the FDA for its refractory forms, the technology has shown significant promise in the treatment of other severe and refractory conditions in a multi-disciplinary setting. Among the major studied conditions are graft versus host disease after allogeneic bone marrow transplantation, systemic sclerosis, solid organ transplant rejection and inflammatory bowel disease.

Materials and methods In order to provide recognized expert practical guidelines for the use of this technology for all indications the European Dermatology Forum (EDF) proceeded to address these questions in the hands of the recognized

experts within and outside the eld of dermatology. This was done using the recognized and approved guidelines of EDF for this task.

Results and conclusion These guidelines provide at present the most comprehensive available expert recommendations for the use of extracorporeal photopheresis based on the available published literature and expert consensus opinion.

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Introduction

Extracorporeal photopheresis (ECP, also known as extracorporeal photochemotherapy, extracorporeal photoimmunotherapy or just photopheresis) is a leukapheresis-based therapy that is available at more than 200 centres worldwide[1]. During ECP, the patient's whole blood is processed outside the body: blood is collected via an ante-cubital vein, or via a permanent catheter if access is cumbersome, and the white blood cells are separated from the red blood cells and plasma by centrifugation in a device that is specifically constructed for the procedure. The white cells are exposed to ultraviolet A (UVA) light in a separate plastic chamber, and then returned to the patient[2]. Initially, when this methodology was rst developed, patients treated with ECP were given oral 8-methoxypsoralen (8-MOP) to produce an effective plasma concentration, and their blood was then leukapheresed[1–3]. This meant that they were still exposed to the gastrointestinal (GI) and ocular side-effects of psoralen, which include nausea and vomiting; moreover, differences in GI absorption due to individual variability[3] resulted in inconsistent blood concentrations of 8-MOP[4]. To avoid the problems associated with oral 8-MOP, the procedure was subsequently modi ed to use a liquid formulation of 8-MOP (UVADEX ; Therakos Inc. West Chester, Pennsylvania, USA), which is added directly to the buffy-coat/plasma blood fraction circulating through the plastic chamber before UVA radiation and re-infusion. This eliminated the side-effects of 8-MOP, as well as the need for pre-medication with this drug and monitoring of its blood levels[4].

The rst investigational study of ECP in cutaneous T-cell lymphoma (CTCL) was completed in 1983[5], and the rst system for ECP, which was a closed system (UVAR, Therakos), was granted approval by the United States Food and Drug Administration in 1988, followed by multiple approvals in Europe and around the world. Although ECP was initially developed for use in CTCL, it has shown promising ef cacy in a number of other severe and dif cult-to-treat conditions, most widely in graft-versus-host disease (GVHD) after allogeneic stem cell transplantation, but also in systemic sclerosis, prevention and treatment of rejection in solid organ transplantation, Crohn's disease and various other diseases[1–6].

Several closed and open ECP systems are now available for clinical use, and some of the currently used approaches are compared in Table 1[7]. In a closed ECP system (i.e. a 'one-step' method), the cell separation, drug photoactivation and re-infusion stages are fully integrated and automated and all the components are validated for use together, tested and approved for use with methoxsalen (Table 2). There is no risk of improper reinfusion when they are used according to their labelling and the risk of infection and contamination associated with the medical device itself is low. Open ECP systems use separate devices for cell separation and drug photoactivation ('two-step' methods), which have not been validated for use together: the combination of a device approved for separation and one approved for photoactivation is not equivalent to a device approved for ECP. Although the components may be CE marked or have FDA approval, they are not speci cally approved for photopheresis (Table 2). As several steps are involved in delivering therapy, there is a potential risk of infection and contamination, as well as a risk of cross-contamination and patient re-infusion error. In general, open systems can only be used by certi ed centres for handling blood components separately, whereas the closed systems do not have this limitation.

Regardless of the system used, treatment with ECP is usually well-tolerated and no severe World Health Organization grade III–IV side-effects have been reported. A few patients may experience transient hypotension during treatment, and mild anaemia and/or thrombocytopenia have also been reported. Some patients are not suitable for treatment with ECP, including those with: a known sensitivity to psoralen compounds such as 8-MOP; comorbidities that may result in photosensitivity; aphakia (UVADEX Sterile Solution is contraindicated in patients with aphakia because of the signi cantly increased risk of retinal damage due to the absence of lenses), pregnancy; history of heparin-induced thrombocytopenia, unsatisfactory cardio-circulatory function and low haematocrit values. In addition, special care needs to be taken in patients with a low bodyweight, in children and in those with problematic venous access. In these contexts, speci c small port systems with an appropriate blood ow per minute should be used.

Ideally, ECP treatment should be initiated as early as possible after the indication is con rmed, which, in most cases, is as second-line therapy after rst-line therapy has failed. At the present time, ECP treatments are generally performed as in-patient therapy in most centres in Europe. Monitoring before and during treatment should be based on the standards of care for each indication. Even though heparin is registered for use with ECP, the use of either heparin or acid citrate dextrose as anticoagulants during ECP can be decided on the basis of the operating prac-

Table 1 ECP approaches in current use in adults and children (adapted from Wong and Jacobsohn[7]).

Methodology	Automated	Weight limit	Cell separator extracorporeal volumes	Cell separator technology
One-step methods				
CELLEX (Therakos®)	Yes (double needle)	RBC prime needed if >115% ECV	Variable, dependent on Hct, blood volume processed, return bag threshold (lower than UVAR XTS)	IFC (continuous buffy coat collection with intermittent uid return) (Latham Bowl)
	Yes (single needle)	RBC prime needed if >115% ECV	Variable, dependent on Hct, blood volume processed, return bag threshold (higher than double needle method)	CFC (Latham Bowl)
UVAR XTS (Therakos)	Yes (single needle)	>40 kg (need to satisfy ECV limits)	Variable, dependent on Hct, number of cycles and bowl size (225 or 125 mL)	IFC (Latham Bowl)
Two-step methods**				
COBE Spectra (Terumo BCT) and UVA irradiator	Yes (only cell separation)	None	282 mL (MNC procedure, Version 4.7); 165 mL (AutoPBSC procedure, Version 6.0)	CFC
Mini-buffy coat and UVA irradiator	No	Smaller children	None, but limited to 5–8 mL/kg whole blood draw	Standard manual buffy centrifugation technique
Three step methods†				
COBE Spectra (Terumo BCT) & UVAR XTS (Therakos)	Yes (only cell separation)	None	See above for MNC and AutoPBSC procedure	CFC

*Suitable for low body weight patients.
** Only cell separation is automated, while the UVA irradiator is operated manually. Other dedicated continuous or intermittent cell separators may also be used such as Amicus (Fenwal, MNC kit), AS104 (Fresnius Kabi) which has extracorporeal volumes of 163 and 175 mL respectively.
†Three-step methods involve standard mononuclear cell collection using dedicated continuous cell separators, followed by red blood cell priming of UVAR-XTS instrument and photoactivation treatment of the 8-methoxypsoralen treated mononuclear cells within the UVAR-XTS instrument after programming the instrument that the last ECP cycle has occurred.
CFC, continuous flow centrifugation; ECV, extracorporeal cell volume; Hct, haematocrit; IFC, intermittent flow centrifugation; MNC, mononuclear cell; RBC, red blood cell.

tices in individual centres and adjusted according to individual patients' medical conditions (e.g. danger of increased bleeding, etc.). While the use of UVA protective glassware is recommended (based on experience with PUVA and oral 8-MOP), it does not appear to be necessary due to the very low levels of psoralen that are used in ECP.

Mode of action

Although ECP has been in clinical use for more than 25 years and is widely used for a variety of clinical entities, the mode of action remains elusive. The original focus included clinical studies and the identification of new indications – as the initial regimen was (by chance) successful, there was lack of incentive to study the mechanism of action to optimize therapy. Indeed, doses and treatment intervals in current use are more or less the same as those used in the 1980s. Early studies indicated that ECP-induced apoptosis in lymphocytes, which in some way contributed to the therapeutic effect.[8,9] More recent studies, most using animal models despite their clinical limitations, have shown the mechanism of action of ECP to be primarily attributable to an immunomodulatory effect – the principal basic mechanisms comprising modulation of dendritic cells, alteration of the cytokine profile, and induction of particular T-cell subpopulations.[10,11]

ECP, like psoralen plus UVA (PUVA), induces psoralen-mediated DNA crosslinks, which cause apoptosis of lymphoid cells, particularly natural killer (NK) and T cells.[12] The therapeutic effect of ECP in Sézary syndrome (SS), however, cannot be explained by depletion of malignant cells, as only a minority of the entire lymphocyte pool is included in a photopheresis cycle. Monocytes treated in the same way appear to be more resistant than lymphocytes to apoptosis, undergoing a differentiation process within 2 days and expressing surface markers that are characteristic of immature dendritic cells (CD83, X-11, Alpha-V, Beta-V, CD1a).[13–15] This differentiation appears to be independent of psoralen-induced photoactivation, and is mostly driven by contact of the cells with plastic and other synthetic materials during passage through the photopheresis system. The apoptotic lymphocytes are phagocytosed and eliminated upon re-infusion. This phagocytosis of apoptotic lymphocytes by immature dendritic cells, which subsequently undergo maturation and present antigenic peptides, has been designated transimmunization.[16] Indeed, it has been suggested that transimmunization induces an immune response against lymphoma cells, which might explain the beneficial effect of ECP in SS.

The ECP-initiated cellular mechanisms of differentiation are associated with the release of a variety of cytokines. These

Table 2 European CE mark and FDA approval status of the 'one-step', closed photopheresis systems and the various cell separation and drug photo activation systems used in the 'two step' photopheresis procedures.

	Company	European CE mark	FDA approval
Closed photopheresis systems			
CELLEX*	Therakos	For photopheresis	For photopheresis
UVAR XTS	Therakos	For photopheresis	For photopheresis
Tubing set (XTS and CELLEX)	Therakos	For photopheresis	For photopheresis
Uvadex	Therakos	For photopheresis	For photopheresis
Cell separation system (standard apheresis device)			
Spectra Optia	Terumo BCT	For therapeutic plasma exchange and white blood cell collection (leucocytes and polymorphonuclear cells)	For therapeutic plasma exchange and leucocytes collection
Cobe Spectra	Terumo BCT	For therapeutic plasma exchange and white blood cell collection (leucocytes and polymorphonuclear cells)	Automated blood cell separator, approved for therapeutic plasma exchange and white blood cell collection (leucocytes and polymorphonuclear cells)
Com.Tec	Fresenius Kabi	For therapeutic plasma exchange and white blood cell collection (leucocytes and polymorphonuclear cells)	For therapeutic plasma exchange and white blood cell collection (leucocytes and polymorphonuclear cells)
MCS plus	Haemonetics	For therapeutic plasma exchange and leucocytes collection	For therapeutic plasma exchange and leucocytes collection
AMICUS	Fenwal	For therapeutic plasma exchange and leucocytes collection	For therapeutic plasma exchange and leucocytes collection
Drug photoactivation system			
PUVA light system	Macopharma	CE marked (indicated to treat psoriasis, not dedicated to ECP)	No
MACOGENIC	Macopharma	UVA illumination machine CE 0459	No
MACOGENIC G2	Macopharma	UVA illumination machine CE 0459	No
XUV bag	Macopharma	UVA illumination machine CE 0459	No
8-MOP	Macopharma	AMM PTA 07.10.109 (indicated for nuclear cell photosensibilisation)	No
UVA PIT system	MedTech Solutions	Medical device for photoimmune therapy	No

*Suitable for low body weight patients.

include tumour necrosis factor (TNF)-α and interleukin (IL)-6, which induce the activation of CD36-positive macrophages.[17] Indeed, it should be pointed out that long-term immunological alterations can be induced by continuous ECP. Depending on its severity, CTCL is associated with an imbalance in the Th1/Th2 immune response, which includes increased release of IL-4 and IL-5, reduced activity of NK cells, and reduced cytotoxicity of CD8-positive T cells. In a study of patients with early-stage CTCL (stage IB) undergoing ECP for 1 year, Di Renzo and colleagues observed not only an increase in CD36-positive monocytes in the peripheral blood but also a change in the cytokine reaction pro le of peripheral blood lymphocytes upon stimulation with phytohaemagglutinin.[18] This implies that ECP reverses the pathologic shift towards a Th2 immune response in CTCL patients and restores the Th1/Th2 balance. In addition, anti-in ammatory cytokines appear to be induced by ECP, whereas pro-in ammatory cytokines are reduced.[19]

Over time, ECP has been shown to be bene cial not only in patients with CTCL but also in those with GVHD, transplant rejection and various autoimmune diseases. The above-mentioned ndings, however, cannot explain the effects of ECP in these patients and, as these conditions respond to immunosuppressive therapies, it was surmised that ECP might also exert inhibitory effects on the immune system. Furthermore, in patients with GVHD, ECP was shown to induce IL-10 via modulation of arginine metabolism.[20] In contrast to immunosuppressive therapy, ECP is not associated with any major side-effects, including opportunistic infections. It has been postulated that the therapeutic effect of ECP operates presumably via the induction of regulatory T (Treg)-cells, without causing general immunosuppression. Using a murine contact hypersensitivity model, Maeda and colleagues demonstrated the induction of Treg-cells by an 'ECP-like' procedure (intravenous injection of leucocytes exposed to 8-MOP and UVA in vitro).[21] Treg-cells induced in this way appeared similar to UVB-induced Treg-cells, which express CD4, CD25, CTLA-4 and the transcription factor Foxp3, and which suppress the activity of other lymphocytes.[22] Furthermore, the release of IL-10 appears to be involved in this

process.[23] A recent study of 46 patients with chronic GVHD (cGVHD) measured serum B-cell activating factor (BAFF) and found that BAFF levels at 1 month after ECP predicted 3- and 6-month skin response, with levels ≤4 ng/mL being associated with a significant skin improvement.[24]

The manifestation of acute GVHD (aGVHD) in patients with allogeneic grafts can be associated with a low number of Treg-cells,[25–28] and induction of T cells with regulatory properties following ECP has been confirmed in a murine GVHD model.[25] Hence, several research groups have studied the effect of ECP on the number of Treg-cells. In the majority of both CTCL and GVHD patients, an increase in Treg-cells was observed, as well as an enhanced suppressive activity.[29–34] This could explain, at least partially, the beneficial effect of ECP in both GVHD and autoimmune diseases, although how this relates to the positive effect of ECP in patients with CTCL remains unknown. In patients with SS, however, reduced numbers of Treg-cells have been observed,[35,36] and their suppressive function appears to be impaired.[37] This has led to speculation on whether Treg-cells have the capacity to suppress CD4-positive tumour cells in patients with SS, and this remains to be determined.

A recent study showed that ECP slightly increased or stabilized the number of peripheral $CD4^+CD25^+FoxP3^+$ Treg-cell counts in lung transplant recipients who showed functional stabilization.[38] Overall, the re-infusion of the treated leucocytes mediated a specific suppression of both the humoral and cellular rejection response, and thereby induced tolerance of the allograft, thus prolonging the survival of transplanted tissues and organs. The mechanism by which ECP counteracts cardiac rejection was studied using a murine model of ECP.[38] Splenocytes exposed to 8-MOP and UVA were injected into syngeneic mice both before and after heterotopic cardiac allograft transplant. None of the mice received immunosuppressive agents. The treatment group showed extended cardiac allograft survival and increased levels of FoxP3-expressing $CD4^+CD25^+$ T cells when compared with controls. The authors concluded that the murine model of ECP extends graft survival in fully histo-incompatible strain combinations with no immunosuppression.[38]

In Crohn's disease, activation of the counterbalancing regulatory response induced by Treg-cells directed against the hyperactive adaptive arm of the immune system could compromise general functionality against pathogenic danger signals. Re-infusion of ECP-generated apoptotic leucocytes back into the patient are hypothesized to generate a tolerogenic response via Treg-cells; indeed, re-circulation of DNA-adduct-positive cells to the intestinal mucosa has been described following ECP.[23,39] Murine models of inflammatory bowel disease have provided information on the potential therapeutic role of Treg-cells in overcoming the disease in humans.[40]

In the only randomized, double-blind, placebo-controlled trial of ECP in children with type 1 diabetes (T1D), the effects of ECP on the immune system were also studied.[41] There were no major effects of ECP on lymphocyte populations. However, in the placebo group, the proportions of activated $CD4^+$ and $CD8^+$ cells increased over time, whereas such changes were not seen in the ECP-treated group. These findings probably reflect an activation of lymphocytes as part of the natural course of T1D and that ECP may have some suppressant effects, preventing lymphocyte activation.[42] ECP produced cytokine changes reflecting a Th2-like response.[43] Placebo-treated patients showed reduced T-cell-associated activity, which seemed to be counteracted by ECP, whereas ECP-treated patients showed preserved T-cell activity. These data indicate that ECP acts to maintain Treg-cell-associated activity in recent-onset T1D.[41]

Although partial aspects of the mode of action of ECP, such as the induction of Treg-cells, are quite clear, we are still far away from a complete understanding of how ECP works. The recent re-establishment of animal models will give the opportunity to modify the ECP procedure with regard to the number of cycles, doses of 8-MOP and UVA, and the number of cells infused, with the ultimate aim of optimizing the regimens that are currently used. In addition, greater understanding of the mechanism of action will finally enable this therapy to be directed towards those patients who could most benefit from it.

Methodology

Guidelines on the use of ECP were identified through a literature search, an internet search of relevant medical databases and a search of relevant professional bodies, as well as expert opinion on the appropriate use of ECP based on 'best medical practices'. The literature evaluated in the existing guidelines, brought up to date with more recently published data, serves as the basis for the present set of guidelines.

ECP is not widely available and is generally used for severe refractory disease courses, or in situations in which other therapies have been tried and have failed. Therefore, the use of this treatment is not generally based on data from controlled and randomized clinical trials, which are usually required for evidence-based medicine, but on multiple small-cohort or case control studies. Double-blinded trials are difficult, and sham photopheresis may be unethical in patients with severe disease.

The guidelines presented here were drawn up to present the indications for which ECP is currently considered as effective, as well as other indications where studies with ECP have shown promising results. For the major indications, namely CTCL and GVHD, the recommendations were developed by a group of experts who are leaders in the development of specific guidelines in these disease areas. For minor indications, expert committees were brought together to examine the available evidence and to make recommendations based on this. The aim was to answer the following questions for each clinical condition:

1 Which diseases are indicated for treatment with ECP?
2 Are there currently any guidelines/consensus statements on ECP in this indication?

3 Which patients should be considered for ECP treatment?
4 What is the optimal treatment schedule and how long should ECP treatment be continued?
5 How is therapeutic ef cacy assessed?

The recommendations were developed and discussed for consensus decision at a number of consensus meetings where the authors and experts were present for reaching consensus agreements (Gothenburg, Sweden, 8 October 2010; Minden, Germany, 24 September 2011; Lisbon, Portugal, 21 October 2011; Geneva, Switzerland, 31 March 2012; Verona, Italy, 8 June 2012 and Prague, Czech Republic, 28 September 2012). The document was circulated among all members of the Guidelines Subcommittee and then the Guidelines Committee for nal approval following the European Dermatology Forum (EDF) standard operating procedures.

Cutaneous T-cell lymphoma

CTCL describes a heterogeneous group of rare lymphoproliferative disorders, which are characterized by the accumulation of malignant T-cell clones that home to the skin.[45] The most common variants are mycosis fungoides (MF), which accounts for about 60% of CTCL cases, and SS, which accounts for 5% of cases. MF is characterized by the presence of a clonal T-cell population in the cutaneous environment and, in the early stages of the disease, presents as scaly patches or plaques, which may resemble eczema or psoriasis in appearance and are often associated with pruritus. As the disease progresses, patients may experience the growth of nodular lesions and large tumours, also with severe pruritus, which may ulcerate and result in chronic septicaemia, thrombosis and pain. SS is the 'leukaemic' form of CTCL, in which the dominant T-cell population also circulates in the peripheral blood and may affect internal organs such as the lungs and spleen. MF/SS is classi ed into clinical stages from IA (the earliest stage) to IVB according to the degree of skin, lymph node, peripheral blood and visceral organ involvement.[46]

Curative therapies are not available and treatment is usually directed towards palliation and the induction of long-term remissions. The aim was to reduce or clear skin lesions, including tumours and reduce pruritus, thereby providing symptom relief and improving patient quality of life.[45] In the early stages of MF, treatment usually involves skin-directed therapies, such as topical corticosteroids, topical chemotherapy (nitrogen mustard or bis-chloronitrosourea) or phototherapy (narrow-band UVB or PUVA). Systemic therapies, including chemotherapy and biological response modi ers [such as interferon (IFN) and bexarotene] are used if the disease progresses, or for those who present with more advanced-stage disease, often in combination with skin-directed therapies.[47]

PUVA, in which patients take an oral formulation of 8-MOP to induce photoactivation followed by exposure of their skin to UVA radiation, is a widely used and effective skin-directed therapy for early-stage, skin-localized CTCL,[47] which can produce relatively long-lived remissions. It is, however, associated with short-term side-effects of oral psoralen intake and possible long-term complications such as photosensitivity and the potential for development of skin cancer.[3] ECP has enabled the safety profile of PUVA to be improved, avoiding the potential complications associated with long-term skin exposure to UVA. It also means that the bene ts of therapy can be extended beyond the treatment of patients with predominantly early disease to patient populations with more advanced disease and the presence of a circulating malignant clone in their peripheral blood.[3]

Many studies have demonstrated that ECP is of signi cant value in the treatment of CTCL. However, because of the rarity of the disease and specialized delivery of therapy, there are no prospective, placebo-controlled, randomized clinical trials that evaluate the impact of treatment on survival, and any comparisons made are usually with 'historical controls'. The initial study of ECP in patients with CTCL resistant to other treatments was reported by Edelson and colleagues in 1987 and showed it to be a promising therapy.[5] Among 37 patients, 27 (73%) responded to treatment, with an average 64% decrease in cutaneous involvement; nine of these patients had a complete response (CR). Data from this study have recently been re-analysed using modern criteria, resulting in a skin overall response rate of 74%, with 33% of patients achieving 50% partial skin response and 41% achieving 90% improvement.[48] An update on the overall survival (OS) of these patients was also provided, which was 9.2 years from diagnosis and 6.6 years from initiation of ECP.

Since 1987, numerous studies have been conducted. A meta-analysis of 19 studies in more than 400 patients at all stages of CTCL reported a combined overall response (OR) rate of 56% with ECP used as monotherapy and 56% when used in combination with other agents, of which 15% and 18%, respectively, were CRs.[49] For erythrodermic disease, the OR rate was 58% and the CR rate was 15%. Importantly, ECP was effective in SS, showing an OR rate of 43%, with 10% CRs. Table 3 (adapted from the UK consensus statement on the use of ECP for the treatment of CTCL and GVHD[50]) provides a summary of the published response rates with ECP in the treatment of CTCL from 1987 to 2011. Based on the 30 separate studies in 689 patients published from 1987 to mid 2007 that were analysed in the UK consensus statement, the mean OR rate in the studies that reported these data was 63% (range 38–100%), and response rates were generally higher among patients with erythrodermic CTCL.[50] The CR rate, where recorded, ranged from 0% to 62% (mean 20%). More recent studies published from late 2007 to 2011[51–57] report OR rates ranging from 42% to 80%, with CR rates ranging from 0% to 30%.

It is clear that ECP is bene cial in the treatment of CTCL, but it is also apparent that there are considerable differences in response rates between centres. Such differences may relate to a number of factors, including differences in patient selection, stage of disease, prior treatments received, ECP protocol used,

Table 3 Summary of studies using extracorporeal photopheresis as monotherapy or in combination with other therapies for the treatment of cutaneous T-cell lymphoma (adapted from Scarisbrick et al. 2008 [50]).

	Patients (n)	OR	CR	PR	MR
Edelson et al.[5]	37 (erythrodermic 29)	73% (27/37) 83% (24/29)	24% (9/37)	35% (13/37)	14% (5/37)
Heald et al.[59]	32 (erythrodermic 22)	NK 86% (19/22)	23% (5/22)	45% (10/22)	18% (4/22)
Nagatani et al.[289]	7	43% (3/7)	NK	NK	
Zic et al.[290]	20	55% (11/20)	25% (5/20)	30% (6/20)	
Koh et al.[291]	34 (erythrodermic 31)	53% (18/34)	15% (5/34)	38% (13/34)	
Prinz et al.[292]	17 (erythrodermic 3)	71% (12/17)	0% (0/17)	41% (7/17)	29% (5/17)
Duvic et al.[293]	34 (erythrodermic 28)	50% (17/34)	18% (6/34)	32% (11/34)	
Gottlieb et al.[60]	28 (erythrodermic NK)	71% (20/28)	25% (7/28)	46% (13/28)	
Stevens et al.[294]	17 (erythrodermic)	53% (9/17)	29% (5/17)	24% (4/17)	
Zic et al.[61]	20 (erythrodermic 3)	50% (10/20)	25% (5/20)	25% (5/20)	
Konstantinow and Balda[295]	12 (erythrodermic 6)	67% (8/12) 50% (3/6)	8% (1/12) 0% (0/6)	42% (5/12) 50% (3/6)	17% (2/12)
Miracco et al.[296]	7	86% (6/7)	14% (1/7)	71% (5/7)	
Russell-Jones et al.[297]	19 (erythrodermic)	53% (10/19)	16% (3/19)	37% (7/19)*	
Vonderheid et al.[298]	36 (erythrodermic 29)	33% (12/36) 31% (9/29)	14% (5/36) 10% (3/29)	19% (7/36) 21% (6/29)	
Zouboulis et al.[299]	20	65% (13/20)	NK	NK	
Jiang et al.[300]	25 (erythrodermic)	80% (20/25)	20% (5/25)	60% (15/25)	
Bisaccia et al.[65]	37	54% (20/37)	14% (5/37)	41% (15/37)	
Crovetti et al.[301]	30 (erythrodermic 9)	73% (22/30) 66% (6/9)	33% (10/30) 33% (3/9)	40% (12/30) 33% (3/9)	
Wollina et al.[302]	20	65% (13/20)	50% (10/20)	15% (3/20)	
Wollina et al.[64]	14	50% (7/14)	29% (4/14)	21% (3/14)	
Bouwhuis et al.[303]	55 SS	80% (44/55)	62% (34/55)	18% (10/55)	
Knobler et al.[304]	20 (erythrodermic 13)	50% (10/20) 85% (11/13)	15% (3/20) 15% (2/13)	54% (7/13)	15% (2/13)
Suchin et al.[62]	47	79% (37/47)	26% (12/47)	53% (25/47)	
Quaglino et al.[305]	19	63% (12/19)	NK	NK	
De Misa et al.[306]	10 (advanced SS)	60% (6/10)	10% (1/10)		
Rao et al.[307]	16	44% (7/16)	NK	NK	
Gasova et al.[308]	8 (2 with CTCL)	100% (2/2)	NK	NK	
Tsirigotis et al.[51]	5 (SS 2)	80% (4/5)	20% (1/5)	60% (3/5)	
Arulogun et al.[52]	13 (all SS; 12 erythrodermic)	62% (8/13)	15% (2/13)	46% (6/13)	
Booken et al.[53]	12 (all SS)	33% (4/12)	0% (0/12)	33% (4/12)	
McGirt et al.[54]	21 (18 erythrodermic)	57% (12/21)	14% (3/21)	19% (4/21)	24% (5/21)
Quaglino et al.[57]	48 (all erythrodermic; 12 MF, 36 SS)	60% (29/48)	13% (6/48)	48% (23/48)	
Raphael et al.[56]	98 (all erythrodermic)	74% (73/98)	30% (29/98)	45% (44/98)	
Talpur et al.[55]	19 (all early-stage MF)	63% (12/19)	11% (2/19)	53% (10/19)	

*Combined PR and MR.

CR, complete response; MF, mycosis fungoides; MR, minor response (≥25% improvement in skin scores); NK, not known; OR, overall response (CR or PR); PR, partial response (≥50% improvement in skin scores); SS, Sézary syndrome.

duration of ECP and the de nition of response that is used.[50] Similar considerations apply to studies reporting survival in patients with CTCL treated with ECP. Variable median survival data have been reported for SS, ranging from 30 months to 60 months,[58,59] which probably re ects the use of different diagnostic criteria. Much longer median survival for CTCL treated with ECP has been reported, but not all patients in the studies had erythrodermic disease or they had received other therapies in combination.[60,61]

The studies listed in Table 3 include ECP used as monotherapy and in combination with other therapies. Such combination therapies have been investigated as a way to further improve response rates, particularly in patients with a high tumour burden. The largest series of CTCL patients treated by ECP was

recently published by Rook and colleagues in the USA, who reported their experience over a 25-year period in 98 erythrodermic CTCL patients treated with at least 3 months of ECP and one or more systemic immunostimulatory agents.[56] A clinically significant improvement was obtained in 75% of patients with this multimodality therapy, with 30% having a CR.

Previously, Suchin and colleagues reported on 47 patients who had received at least 6 cycles of ECP: 68% had stage III or IV CTCL and 89% had circulating malignant T cells.[62] Thirty-one patients received treatment with ECP and one or more other systemic agents, including IFN-a, IFN-c, granulocyte–macrophage colony-stimulating factor (GM-CSF; sargramostim) or systemic retinoids, for 3 months or more. Overall, 79% of patients responded to therapy, with 26% having a CR. Among patients receiving combination therapy, 84% achieved a response, with 20% having a CR, whereas the OR rate with ECP monotherapy was 74%, of which 38% were CRs. The median survival was 74 months with combination therapy vs. 66 months for ECP monotherapy, although the difference was not statistically significant.

A prospective observational study in 48 patients with erythrodermic CTCL (36 with SS) reported a response rate of 58% with ECP alone, compared with 64% with combination therapy in patients with more adverse prognostic factors.[57] Similarly, Duvic and colleagues reported a slightly higher response rate among patients treated with ECP in combination with IFN-a, bexarotene or GM-CSF compared with 54 who had received ECP monotherapy (OR> 50% in 56% vs. 43% respectively).[63] A number of other studies with ECP plus IFN-a have been published that report an increased response rate compared with ECP monotherapy.[60,64,65] However, none of these studies was controlled or randomized, making it difficult to assess how much of the clinical benefit was due to IFN-a and how much to ECP, and what synergistic effects can be obtained.

ECP has also been used in combination with total skin electron beam (TSEB) therapy. A retrospective study of 44 patients with erythrodermic MF/SS treated with TSEB with or without ECP reported an overall CR of 73% with a 3-year disease-free survival of 63%.[66] Among those receiving combined TSEB and ECP, the 3-year disease-free survival was 81% compared with 49% with TSEB alone. On the basis of these data, further studies with the TSEB and ECP combination are warranted.

Most of the studies with ECP in CTCL have primarily included patients with advanced stages of the disease. Guidelines recommend ECP as first-line systematic therapy for erythrodermic MF and SS.[47,50,67–69] Its use in early stages of CTCL is controversial but warrants further investigation. A literature review of data from 16 studies with ECP or ECP plus adjuvant therapy from 1987 to 2007, which included a total of 124 patients with early-stage (stage IA, IB, IIA) CTCL, found that the response rates ranged from 33% to 88% if ECP was used as monotherapy and from 50% to 60% with ECP plus adjuvant therapy.[70] Furthermore, many early-stage patients treated with ECP achieved long-lasting regression of disease. In a recent study, 19 patients with early-stage MF were treated with ECP on two consecutive days every month for 6 months.[55] Patients with a partial response (PR) continued with ECP alone for 6 months, whereas non-responders could receive additional therapy with oral bexarotene and/or IFN-a. The OR rate for ECP alone was 42% (8/19, including 1 CR; 7 PR), with an overall duration of response of 6.5 (range 4–18) months. Seven patients with stable disease at 3 months received additional bexarotene and/or IFN-a and four (57%) responded. For all 19 patients, the OR rate was 63% (2 CR, 10 PR). Most guidelines do not indicate use of ECP in early stage disease, but the National Comprehensive Cancer Network (NCCN) Guidelines recommend ECP in those patients with stage IA, IB and IIA refractory disease.[69]

In summary, for patients with advanced CTCL (such as those with erythroderma or the presence of peripheral blood involvement), which are typically resistant to treatment and weighted by a poor prognosis, ECP, either as monotherapy or combined with other immunotherapies, offers good treatment efficacy and the possibility of prolonged survival. Given the very low side effect profile of ECP compared with other therapies and its demonstrated efficacy in later-stage CTCL, this treatment modality is possibly also beneficial in earlier stages of the disease, as recently suggested,[55] although further studies that focus on this patient population are needed. There is, however, inter-patient variability in the response to ECP in CTCL, so attempts have been made to characterize those patients who are most likely to be responders. The prognostic factors that have been identified include the following[50,70,71]:

- short duration of disease, preferably <2 years;
- absence of bulky lymphadenopathy or major internal organ involvement;
- white blood cell count <20 000 mm^3;
- presence of a discrete number of Sézary cells (10–20% of mononuclear cells);
- natural killer cell activity close to normal;
- cytotoxic T lymphocytes close to normal (CD8+ 15%);
- absence of prior intensive chemotherapy; and
- plaque stage disease not covering more than 10–15% of total skin surface.

Although these criteria are useful in identifying the likely best responders to ECP, they are not absolute, and some patients who fall outside these criteria will also respond.[71] A critical factor for success is that the patient must be able to mount an immune response against the malignant cells that have passed through the photoactivating device.[72,73]

Existing clinical guidelines

Several professional organizations have produced guidelines on the management of CTCL and the use of ECP.

In the European Organization for Research and Treatment of Cancer (EORTC) consensus recommendations for the treatment

of MF/SS (published in 2006),[47] ECP was recommended for the first-line treatment of MF stage III and for first-line treatment of SS, with a strength of recommendation of C (on a scale from A to D). In MF, the level of evidence was rated as 4 (evidence from case series, poor-quality cohort or case–control studies) and in SS as 2b (evidence from individual cohort study or poor-quality, randomized, controlled trial). Although not a recommendation, it was mentioned that the usual ECP treatment schedule was two successive days every 4 weeks, continued for up to 6 months, followed by maintenance therapy tailored according to disease course and severity.

The UK Photopheresis Expert Group consensus statement[59] on the use of ECP is a comprehensive document published in 2008, which, after reviewing the literature, recommended that ECP should be considered for the treatment of patients with CTCL who fulfil both of the major criteria of erythroderma and stage III or IVA CTCL (histology consistent with CTCL), as well as one of the minor criteria: circulating clonal disease (circulating T-cell clone by polymerase chain reaction or Southern blot analysis); evidence of circulating Sézary cells > 2 (10% of circulating lymphocytes); CD4/CD8 ratio > 10. The recommended treatment cycle was one cycle (i.e. two consecutive days) every 2–4 weeks (to be given more frequently in symptomatic patients and in those with a high peripheral blood tumour burden). Treatment should be tapered at maximal response or greater to one cycle every 4–12 weeks before stopping. Guidance was provided on monitoring treatment, and assessments at 3-monthly intervals were recommended, to allow non-responders to be offered combination or alternative therapy and to ensure that ECP treatment was not prolonged to the detriment to their health, and to avoid ECP being given alone for more than 6 months in patients with responses of less than 50%.

The British Photodermatology Group and UK Skin Lymphoma Group published a report in 2006 on evidence-based practice of ECP based on data from 1987 to 2001,[74] which looked at the use of ECP in a variety of conditions. They concluded that there was: 'fair' evidence that ECP has clinical benefit in erythrodermic MF/SS (stage III/IVA/B1/0), with a strength of recommendation of B (on a scale from A to E), based on level II-i evidence (i.e. from well-designed controlled trials without randomization); 'fair' evidence to support the use of TSEB with ECP for erythrodermic MF/SS [strength of recommendation B, quality of evidence II-ii (well-designed cohort or case–control studies)]; and poor evidence to support the use of IFN-α plus ECP for erythrodermic MF/SS (strength of recommendation C, quality of evidence II-ii). The authors described a typical protocol of two ECP treatments on two consecutive days per month, continued for up to 6 months, followed by tapering or maintenance treatment in those patients who have responded. The frequency of treatment can be increased to fortnightly in poor responders, or ECP can be combined with other therapeutic agents such as IFN-α. Recommended patient assessments and appropriate efficacy parameters were also listed.

The National Cancer Institute in the USA guidance on treatment of MF and SS[68] listed appropriate treatments at each CTCL disease stage. ECP was included as an option for the treatment of stage III MF/SS and, either alone or with TSEB, for the treatment of stage IV MF/SS. For patients with recurrent MF/SS, it was noted that ECP has produced tumour regression in those who are resistant to other therapies. No information was given on the appropriate monitoring of therapy or of outcomes.

The NCCN clinical guidelines on MF/SS (2012) state that their recommendations are all based on category 2A evidence (lower level evidence but with NCCN consensus). ECP was recommended as first line for stage IV SS, alone or in combination with interferon or bexarotene. ECP was also recommended in relapsed or refractory stage III disease and in IA–IIA disease refractory to skin-directed therapy.[69]

The United States Cutaneous Lymphoma Consortium (USCLC) reviewed the therapeutic options for SS.[75] ECP was recommended as a category A systemic monotherapy, based on level IV-2 evidence (i.e. obtained from at least one prospective, well-designed cohort or case–control study, preferably from more than one centre or research group). In addition, recommended category A combination therapies included TSEB plus ECP alone or in combination with IFN-α, IFN-γ or bexarotene, and ECP plus bexarotene, IFN-α, IFN-γ or low-dose methotrexate singly or in combination.

The NORth Trent COMmissioners (NORCOM) policy on ECP for cancer and disease (reviewed in 2008)[76] was developed to provide guidance to five UK Primary Care Trusts on when ECP therapy should be funded. It concluded that, based on case series studies alone (i.e. lower quality evidence than randomized controlled trials), the evidence supports the use of ECP for erythrodermic MF/SS. They recommended that, to be eligible for treatment, patients with CTCL should fulfil all the following criteria: erythroderma, biopsy-proven diagnosis of CTCL, evidence of circulating clonal disease and evidence of circulating Sézary cells (10% of lymphocytes present). The recommended treatment was two consecutive days of ECP per month for a minimum of 6 months. Recommendations were also provided on monitoring of therapy, response assessment criteria and tapering of treatment in responders.

Finally, the Association of the Scientific Medical Societies of Germany recently provided guidance on the staging, assessment, diagnosis and therapy of cutaneous lymphomas.[77] ECP was recommended as first-line treatment for erythrodermic MF stage III, and for SS. The guidelines stated that ECP could be combined with IFN-α, methotrexate, bexarotene or PUVA, and they also commented on the good safety profile of ECP. No rating of the grade of recommendation or level of evidence was given, and no information was provided on how the guidelines were prepared.

Recommendations

Patient selection ECP should be considered as first-line therapy for the following CTCL patients.

- Erythrodermic stage IIIA or IIIB (i.e. with B0 or B1 score according to the revised International Society for Cutaneous Lymphomas [ISCL]/EORTC classification).[46]
  Even though a series of papers (see the recent study by Talpur et al.[55]) have suggested that there is a potential benefit of ECP in patients with early-stage disease (stage IA, IB, IIA), the consensus decision was that this indication should be considered only for clinical trial purposes, as a variety of other safe, effective and easily accessible treatment options are available for use at this stage.
- Stage IVA1 (i.e. patients with B2 score) and a T score of T1, T2 or T4.
- Stage IVA2 (i.e. patients with N3 score) and a T score of T4.

Treatment schedule

- Initial recommended schedule should be one cycle (i.e. two consecutive days) every 2 weeks for the first 3 months, then once monthly or every 3 weeks. However, there is no clear optimal therapy, and other published guidelines have recommended one cycle every 1–2 weeks, followed by tapering after maximum response.[50]
  There are no controlled data in the literature that clearly support higher clinical activity associated with more frequent ECP courses. On the basis of clinical experience, it was recognized that an initial increased frequency of treatment courses could give a potentially significant benefit, particularly in patients with strong subjective symptoms (itchiness) and those with B2 score. However, based on patient compliance, a standard monthly treatment could also be performed, according to the policies and possibilities at each centre.
- Treatment should be continued for a time period of not less than 6 months, and ranging between 6 and 12 months to evaluate for a positive response.
- At maximal response, treatment should be slowly tapered to one treatment every 4–8 weeks for maintenance therapy.
- In patients with a response or disease stabilization and good quality of life, ECP treatment should not be stopped and should be prolonged for even more than 2 years, with a progressive extension of treatment intervals up to 8 weeks.
- Patients who do not respond to ECP as first-line therapy should be considered for combination therapies (i.e. ECP plus other drugs).
- The agents that should be associated with ECP on the basis of their known immunomodulatory mechanisms are IFN and/or bexarotene.
  Skin care and topical medications need to be included from the start of ECP. In addition, topical steroids applied on selected parts of the body skin surface are allowed in association with ECP, particularly in patients with strong subjective symptoms.
  In patients with a frank 'leukaemic' involvement with high white blood cell counts (i.e. >20 000 mm^3), cytoreductive treatment (debulking chemotherapy or alemtuzumab) can be performed before ECP to decrease the extent of peripheral blood involvement. Also, local radiotherapy can be performed either before or during ECP to treat localized infiltrated lesions. While the association of ECP with histone deacetylase inhibitors appears potentially useful, at present there are no published data available to support this combination.
- Systemic concurrent therapies can be initiated at any time point at the discretion of each centre; however, it is suggested to wait for at least 3 months of ECP monotherapy before starting an associated drug. If patients are already on other therapies (bexarotene and/or IFN), then ECP can be added without the withdrawal of the previous treatment.

Response assessment

- Response assessment should be performed every 3 months and made on the basis of the ISCL/USCLC/EORTC consensus statement.[78] It is recommended to wait for at least 6 months of treatment before concluding that ECP is not effective. Based on clinical experience, responses usually do not develop early and can also be observed a considerable period of time after starting ECP. It was agreed that the minimum time for evaluation of response to ECP should be after at least 6 months of treatment before it is concluded that ECP is not effective.
- In the presence of a CR, treatment should not be stopped and prolonged for a long period of time, with a progressive extension of treatment intervals up to 8 weeks.
- In the presence of PR/stable disease, it is suggested to evaluate for combination treatments or to increase the frequency of treatments.
- In the presence of progressive disease, it is suggested to evaluate for combination treatments, to increase the frequency of treatments, or to stop ECP in favour of alternative anti-CTCL therapy.

Chronic graft-versus-host disease

cGVHD is a serious complication of allogeneic haematopoietic stem cell transplantation (HSCT), associated with substantial morbidity and mortality, mainly due to infectious complications.[79–81] First-line therapy of cGVHD consists of corticosteroids,[82–84] whereas many therapeutic options have been reported for salvage therapy.[85,86] However, no single class of immunosuppressive agent has consistently achieved a steroid-sparing effect in patients with cGVHD.

Table 4 Summary of studies using extracorporeal photopheresis in paediatric patients with chronic graft-versus-host disease.

	Patients (n)	CR/PR skin	CR/PR liver	CR/PR oral	Comment
Rossetti et al.[87]	7	33% (2/6)	100% (1/1)	–	50% (2/4) lung CR
Dall'Amico et al.[88]	4	67% (2/3)	–	–	67% (2/3) lung improved
Salvaneschi et al.[89]	14	83% (10/12)	67% (6/9)	67% (8/12)	79% OS
Halle et al.[90]	8	88% (7/8)	67% (4/6)	–	100% OS
Perseghin et al.[91]	9	88% (7/8)	100% (2/2)	67% (2/3)	–
Perutelli et al.[92]	7	–	–	–	43% (3/7) CR; 57% (4/7) improved
Messina et al.[93]	44	56% (20/36)	60% (12/20)	–	77% OS
Duzovali et al.[94]	7	–	–	–	43% (3/7) improved; 43% (3/7) died
Kanold et al.[95]	15	75% (9/12)	82% (9/11)	86% (6/7)	67% (10/15) alive
Perseghin et al.[96]	25	67% (4/6)	67% (4/6)	78% (7/9)	76% (19/25) alive
Gonzales-Vicent et al.[97]	3	100% (2/2)	100% (2/2)	–	100% (3/3) alive
Perotti et al.[98]	23	96% (22/23)	100% (4/4)	80% (4/5)	83% (19/23) alive at 5 years

CR, complete response; OS, overall survival; PR, partial response.

ECP represents a frequently used therapeutic approach for the treatment of cGVHD. Recently, Martin and colleagues, performing a comprehensive review of both retrospective and prospective trials of cGVHD therapy, reported on 60 studies evaluating 17 different agents.[86] Interestingly, ECP was the most frequently studied therapy. Tables 4[87–98] and 5[99–108] provide a summary of studies with ECP in paediatric and adult patients with cGVHD.

Owsianowski and colleagues reported the first use of ECP in cGVHD in 1994,[109] and it is now a widely recognized second-line therapy for cGVHD patients failing on corticosteroids.[85,110]

Table 5 Summary of studies using extracorporeal photopheresis in adult patients with chronic graft-versus-host disease.

	Patients (n)	CR/ PRskin	CR/ PRliver	CR/ PRoral	OR
Greinix et al.[99]	15	80%	70%	100%	NK
Apisarnthanarax et al.[100]	32	59%	0%	NK	56%
Seaton et al.[101]	28	48%	32%	21%	36%
Foss et al.[102]	25	64%	0%	46%	64%
Rubegni et al.[103]	32	81%	77%	92%	69%
Couriel et al.[104]	71	57%	71%	78%	61%
Greinix et al.[105]	47	93%	84%	95%	83%
Flowers et al.[106]	48	40%	29%	53%	
Dignan et al.[107]	82	92%	NK	91%	74%
Greinix et al.[108]	29	31%	50%	70%	NK

CR, complete response; NK, not known; OR, overall response; PR, partial response.

The safety profile of ECP is excellent, with minimal side-effects and no long-term complications, particularly in comparison with other immunosuppressive therapies currently available for cGVHD (including mycophenolate mofetil, tacrolimus, inhibitors of the mammalian target of rapamycin, hydroxychloroquine and rituximab), which are known to be associated with increased organ toxicities, susceptibility for opportunistic infections and relapse of original disease.[85] Most of the evidence on the use of ECP in cGVHD comes from patients with steroid-refractory disease and there are very few data currently available for the use of ECP as a first-line therapy of cGVHD.[84] Due to the excellent safety profile of ECP and frequently reported evidence that the graft-versus-leukaemia effect seems not to be impaired by ECP, leading experts in the field of allogeneic HSCT recommend the use of ECP earlier in the course of cGVHD.[95,105,111]

Most countries perform ECP in specialized centres and offer it as a second- or subsequent-line therapy for patients with steroid-refractory, -dependent or -intolerant cGVHD in need of systemic therapy.[85,89,93,98,102,104–107,112–114] Flowers and colleagues published the first multicentre, randomized, controlled, prospective phase II trial of ECP in 95 patients with steroid-refractory/-dependent/-intolerant cGVHD.[106] The primary efficacy end-point of the study was a blinded quantitative comparison of percentage change from baseline in Total Skin Score (TSS) of 10 body regions at week 12. The median percentage improvement in TSS at week 12 was 15% for the ECP arm compared with 9% for the control arm, a non-significant difference. However, significantly more patients in the ECP arm had a complete or partial skin response, as assessed by the clinical investigators ($P < 0.001$). At week 12, the proportion of patients who had at least a 50% reduction in steroid dose and at least a 25% decrease in TSS was 8% in the ECP arm vs. 0% in the control arm ($P = 0.04$). A steroid-sparing effect of ECP has also been reported by other investigators.[89,99,102,104,105,108,115] In a subsequent prospective clinical study, 29 patients in the control group

not responding to conventional immunosuppressive treatment in the initial randomized study were eligible for open-label ECP in case of progression of cutaneous cGVHD or less than 15% improvement in the TSS by week 12.[108] Besides achieving a complete or partial skin response at week 24 of ECP treatment in nine patients (31%), response in extracutaneous manifestations of cGVHD, including oral mucosa, eyes, liver and lung, was observed in 70%, 47%, 50% and 50% of patients by week 24, respectively.

Organ involvement is a main parameter predicting response to ECP. Investigators consistently report best responses in skin (both lichenoid and sclerodermoid), mucous membrane and liver manifestations of cGVHD. In 2007, Scarisbrick and colleagues reviewed 23 individual studies including 633 patients with cGVHD given ECP between 1987 and 2001.[50] The response rates were recorded according to involved organ. The mean response rate in cutaneous cGVHD, as reported in 18 studies, was 68% (range 29–100%), including CRs in some patients. The mean response rate in patients with hepatic involvement, as reported in 10 studies, was 63%. The mean response rate in patients with mucosal involvement, as reported in 9 studies, was also 63%.

Experience is limited with ECP in other manifestations of cGVHD, such as lung involvement, with 100 reported patients achieving a response rate of 51%, including 14 CRs, 20 PRs and 17 improvements.[93,104,106,108,116–118] In view of the dismal prognosis of pulmonary cGVHD and the limited therapeutic options for these patients, results of ECP in pulmonary cGVHD are encouraging. Nonetheless, the efficacy of ECP in lung manifestations of cGVHD needs to be determined in prospective studies with a larger patient cohort. Considering its excellent safety profile, ECP should be administered earlier in the course of cGVHD to avoid irreversible tissue damage and patient mortality due to infections during immunodeficiency. ECP has steroid-sparing properties and may prevent adverse effects from prolonged immunosuppression.[106] Of note, ECP reportedly does not cause generalized immunosuppression,[62] and no increase in infectious complications has been reported during ECP therapy.[99,105,106,119]

Many investigators administer ECP in patients with cGVHD according to the original publication by Edelson and colleagues.[5] This consists of two ECP treatments on consecutive days every 2–4 weeks. Typically, therefore, cGVHD has been treated with 4–8 treatments per month, usually for 12–24 weeks.[99,105,112] There is little evidence as to the value of increased ECP treatments in this initial phase. In a prospective, phase II study, Foss and colleagues found no advantage for patients initially treated with a more intensive weekly schedule compared with those receiving biweekly treatment.[102] Subsequent prolongation of the interval between ECP treatments is typically performed by many centres. However, only limited data are currently available on the advantages and disadvantages of ECP tapering, and thus no recommendations can be provided. Tapering is in uenced in most series by the ability to reduce concurrent immunosuppressive therapy, regarded as a signi cant risk factor for infection-related morbidity and mortality. Progression of cGVHD under treatment is an indication for discontinuation of ECP, whereas recurrence of cGVHD during tapering or after discontinuation of therapy may be controlled by restarting ECP or intensi cation of the treatment schedule with a subsequently slower weaning regime.[50]

The length of therapy required for individual patients is difficult to predict from current published literature, in view of the diversity of treatment schedules applied and the difficulty in comparing heterogeneous patient populations.[89,93,99,101,104,105,113] Dignan and colleagues reported on 82 patients who received a bimonthly regimen of two ECP treatments on consecutive days (one cycle), which was subsequently tapered to a monthly regimen depending on response.[107] The median duration of treatment was 330 (range 42–887) days and the median number of ECP cycles received was 15 (range 2–125 cycles. Eighty-four per cent of patients completed a minimum of 6 months of treatment. Among those receiving immunosuppressive drugs at the start of ECP treatment, 77% had a dose reduction after 6 months of treatment and 80% had reduced their steroid dose. However, in the largest retrospective study published to date, from the MD Anderson Cancer Centre, the median number of ECP treatments administered was 32 (range 1–259) over a median of 14.5 (range 3–133) weeks.[104] Foss and colleagues observed an OR rate of 64%, defined as response in at least one site of disease, when ECP was given to 25 patients with extensive steroid-refractory cGVHD.[102] The median duration of therapy was 9 (range 2–24) months. In line with these findings, Greinix and colleagues reported complete resolution of cutaneous features in 12 of 15 patients (80%) with steroid-refractory extensive cGVDH who were given ECP for a median of 12 (range 4–31) months.[99] In the recently published prospective study in 29 patients with steroid-refractory cGVHD, progressive improvement in the TSS during weeks 16 and 24 of open-label ECP treatment was observed, suggesting a cumulative response over time.[108] These findings and the higher response rates reported in other studies with prolonged treatment with ECP[99,100,102] suggest that continuation of ECP beyond 24 weeks may result in further benefit in patients with longer duration of cGVHD. Of note, longer treatment duration may also be necessary to obtain best responses to ECP in patients with sclerodermatous manifestations.[99,100,104,120]

Survival rates are variable among reports in the literature. Significantly improved survival rates and improvements in quality of life in ECP responders have been reported by Greinix and colleagues[99,105] and Messina and colleagues.[93] In the prospective, randomized study on steroid-refractory/-dependent/-intolerant cGVHD patients, ECP treatment was significantly associated with improved quality of life, demonstrated by a 19% improvement in the median targeted symptom assessment scores in the ECP arm

compared with a 3% improvement in the control arm (P = 0.01).[106]

Kanold and colleagues treated 15 paediatric patients with steroid-refractory cGVHD, achieving high response rates in those with cutaneous (75%), hepatic (82%) and mucosal (86%) involvement.[114] Steroids could be tapered by 50% after a median of 12 (range 4–23) procedures, and could be discontinued during ECP in three patients. After a median follow-up of 52 (range 6–108) months, 10 of the 15 patients (67%) were alive. Tolerance of ECP was generally good, the main limiting factors being vascular access and the psychological impact of repeated aphaeresis procedures. Furthermore, children weighing less than 25 kg were not any more susceptible to side-effects compared with patients weighing more than 25 kg.

In summary, ECP is a safe and efficacious form of cGVHD therapy, with steroid-sparing capacity. A venous access for therapy is required and peripheral veins should be used preferentially to avoid central line-associated infections. Further prospective clinical studies are warranted to assess the efficacy of ECP in homogeneous cohorts of cGVHD patients treated earlier in the course of disease.

Existing clinical guidelines

In 2008, Scarisbrick and colleagues[50] published a UK consensus statement on the use of ECP for the treatment of cGVHD. In this statement, it was decided that ECP should be considered for patients with cGVHD who are refractory to, dependent on, or intolerant of corticosteroids.

Recently, recommendations of a joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMT) have been published, based on review of the available literature.[110] In these guidelines, ECP was strongly recommended (grade 1b) as second-line therapy for skin, oral and liver manifestations of cGVHD, with a schedule of fortnightly paired treatments for a minimum assessment period of 3 months. Grade 1 recommendation means that there is confidence about the benefits of ECP and no other immunosuppressive therapeutic modality received a stronger recommendation for second-line therapy of cGVHD. Furthermore, ECP was recommended as a third-line treatment option in cGVHD involving other organs (grade 2C). It was observed that infections requiring systemic antibiotics may be halved in patients receiving ECP.

The German/Austrian/Swiss consensus conference on second-line treatment of cGVHD in daily clinical practice recommended ECP with a strength of recommendation of C-I, meaning use in second-line treatment is justified, based on grade II evidence.[85] Of note, ECP was considered superior to other novel immunosuppressive agents, due to its excellent safety profile and steroid-sparing effect. These recommendations were based on the fact that numerous investigators had reported high response rates in skin, liver and oral manifestations of steroid-refractory cGVHD and improved survival rates both in children and in adults. Considering the use of ECP in the first-line treatment of cGVHD, the German/Austrian/Swiss consensus conference stated that, while ECP has been found to be associated with a steroid-sparing capacity and favourable side effect profile, there are currently insufficient data to support the use of ECP in first-line treatment but that further studies are highly warranted.[85]

In 2007, Kanold and colleagues published clinical practice guidelines on the use of ECP in children with cGVHD after allogeneic marrow transplantation, based on field experience and a review of the literature.[95] In these guidelines, ECP was recommended in paediatric patients with cGVHD not responding to steroids, defined as stable disease after 1 month of steroid treatment, PR after 2 months of steroids, or progression of cGVHD after 2 weeks of steroid treatment. Thus, ECP was recommended as second-line therapy of cGVHD not responding to corticosteroids. Furthermore, ECP was recommended in paediatric patients with severe cGVHD with steroid-intolerance, and in steroid-refractory or steroid-dependent paediatric patients after more than three lines of immunosuppressive therapies. In view of the excellent safety profile of ECP, Kanold and colleagues considered ECP as first-line therapy for paediatric patients with limited cGVHD regardless of other therapies administered.

Recommendations

Patient selection Patients with moderate or severe cGVHD according to National Institutes of Health (NIH)-defined criteria[121] should receive systemic therapy. Mild manifestations of cGVHD that cannot be treated sufficiently by topical agents, such as hepatic manifestations or fasciitis, may also be treated with systemic corticosteroids for first-line therapy. Currently, no uniformly accepted definition of steroid-refractory cGVHD is available and generally accepted criteria include progression on prednisone at 1 mg/kg/day for 2 weeks, stable disease on at least 0.5 mg/kg/day for 4–8 weeks and inability to taper steroids below 0.5 mg/kg/day.[85]

For second-line therapy of steroid-refractory cGVHD, all patients are eligible to receive ECP, except those with total leucocyte counts below 1.0 G/L, intolerance to methoxsalen, heparin or citrate products, and hemodynamic instability due to ongoing life-threatening infections or severe bleeding events.

Treatment schedule No general recommendation can be made on treatment schedule, due to missing evidence. Typically, patients would receive one cycle of two ECP treatments every 1–2 weeks for weeks 1–12. After week 12, treatment intervals could possibly be increased by 1 week every 3 months, depending on the type of lesions, extent of cGVHD and clinical response. If cGVHD progresses, a change in treatment strategy should be considered.[84,85]

Response assessment Response should be assessed according to the NIH guidelines.[122]

Acute graft-versus-host disease

aGVHD, like cGVHD, is a serious complication of allogeneic HSCT, and a key cause of transplant-related morbidity and mortality, mainly due to severe infections and organ toxicities.[123] Furthermore, aGVHD is an important risk factor for the later development of cGVHD. Currently, standard first-line therapy consists of corticosteroids; however, only up to 50% of all patients respond to therapy and thus a substantial proportion of patients with aGVHD require salvage treatment.[123–126] So far, no immunosuppressive agents have been approved for the treatment of steroid-refractory aGVHD. Despite many studies, practices vary considerably regarding the selection of agents for treatment of steroid-refractory aGVHD. Recently, Martin and colleagues published recommendations of the American Society of Blood and Marrow Transplantation for the treatment of aGVHD based on a comprehensive and critical review of published reports.[123] Across the 67 studies selected with well-defined evaluation criteria, 19 different agents were investigated. Besides horse antithymocyte globulin (ATG), ECP was the most frequently studied therapeutic option. Approximately, 300 patients with steroid-refractory aGVHD given ECP have, so far, been reported in numerous publications, with an increasing number during recent years.[89,93,95,97–99,113,114,116,119,127–135] Overall, CR and PR of cutaneous manifestations were observed in a median of 75% (range 50–100%) of patients, CR and PR of hepatic involvement were observed in a median of 47% (range 0–100%) of patients, and CR and PR of GI manifestations were observed in a median of 58% (range 0–100%) of patients. ECP was tolerated excellently and side-effects were mild, consisting mainly of reversible drops in peripheral blood cell counts after the first courses of ECP.

The results of studies with ECP in the second-line treatment of aGVHD are summarized in Table 6.[88,89,93,95,97,98,116,129–131,133] Following promising results in preliminary investigations,[99] then in a pilot study of 21 patients,[119] Greinix and colleagues conducted a phase II study of ECP in 59 adult patients with severe aGVHD (both steroid-refractory and steroid-dependent).[129] CR rates for individual organs were 82% for skin involvement and 61% each for GI and liver involvement. Responses were highest in patients with cutaneous symptoms only (87%), and lower for those who had two organ systems involved (62% for skin and liver involvement, 40% for skin and GI involvement), or those who had all three organs affected (25%). Response rates were also higher for patients with less severe grades of aGVHD at the start of treatment (CR rate 86% for grade II, 55% for grade III and 30% for grade IV aGVHD). In contrast to the pilot study,[119] an intensified schedule of ECP was administered in the phase II study, consisting of two to three treatments per week on a weekly basis until maximum response. This strategy led to improvements in CR rates in patients with grade IV aGVHD (60% vs. 12%) and GI involvement (73% vs. 25%) using the intensified ECP schedule compared with the pilot study.[128,129] Best response to ECP was observed after a median of 1.3 (range 0.5–6.0) months of treatment and no flare-ups were seen after tapering and discontinuation of corticosteroids. In ECP-responding patients, corticosteroids could be discontinued after a median of 55 (range 17–284) days after the start of ECP. In univariate analysis, a lower grade of aGVHD and fewer organs involved at the start of first-line therapy with corticosteroids as well as at the start of ECP, and a lower cumulative corticosteroid dose prior to ECP, significantly increased the probability of CR of steroid-refractory aGVHD with ECP. However, in logistic regression analysis, only a lower grade of aGVHD at the start of ECP and later onset of corticosteroid medication after HSCT were variables significantly favouring the achievement of CR by ECP. The cumulative incidence of transplant-related mortality at 4 years was 14% in patients achieving a CR of steroid-refractory aGVHD, compared with 73% in patients without CR, 3 months after the start of ECP ($P < 0.0001$). Patients with a CR of steroid-refractory

Table 6 Summary of studies using extracorporeal photopheresis in the second-line treatment of acute graft-versus-host disease.

	Patients (n)	CR skin	CR liver	CR gut	OS
Salvaneschi et al.[89]	9	67% (6/9)	33% (1/3)	60% (3/5)	67%
Dall'Amico et al.[116]	14	71% (10/14)	57% (4/7)	60% (6/10)	57%
Messina et al.[93]	33	76% (25/33)	60% (9/15)	75% (15/20)	69% at 5 years
Garban et al.[130]	12	67% (8/12)	0% (0/2)	40% (2/5)	42%
Greinix et al.[129]	59	82% (47/57)	61% (14/23)	60% (9/15)	47% at 5 years
Kanold et al.[95]	12	90% (9/10)	56% (5/9)	83% (5/6)	75% at 8.5 months
Calore et al.[133]	15	92% (12/13)	-	100% (14/14)	85% at 5 years
Gonzales-Vicent et al.[97]	8	100% (8/8)	100% (2/2)	57% (4/7)	38%
Perfetti et al.[131]	23	65% (15/23)	27% (3/11)	40% (8/20)	48% at 37 months
Perotti et al.[98]	50	83% (39/47)†	67% (16/24)†	73% (8/11)†	64% at 1 year

†Combined CR and PR.

CR, complete response; OS, overall survival; PR, partial response.

aGVHD with ECP had a significantly improved OS of 59%, compared with 11% in patients without a CR ($P < 0.0001$). The cumulative incidence of relapse at 4 years was 28%, which was thus not increased when compared with HSCT patients not receiving ECP. Treatment with ECP was well tolerated and no increase in rates of infection was observed.

Perotti and colleagues recently reported excellent response rates in 50 patients with steroid-refractory aGVHD and confirmed the corticosteroid-sparing effect of ECP.[98] There was a policy of early intervention in patients with aGVHD, so the median time from onset of symptoms to start of ECP therapy was 9 days. The OR rate was 68% (32% CR and 36% PR), with similar response rates for the different organ systems (83% skin, 67% liver, 73% GI system). Furthermore, ECP-responders had a significantly improved survival of 62%, compared with 6% in aGVHD patients not responding to ECP ($P < 0.001$). Ability to decrease the corticosteroid dose 30 days after the start of ECP was associated with significantly decreased mortality, confirming the importance of corticosteroid-sparing in aGVHD. Other authors have also noted that the possibility of reducing or discontinuing immunosuppressive therapies, and particularly ongoing corticosteroids, is a major advantage for ECP in preventing long-term complications in children.[93,95]

Several studies of ECP have been conducted in paediatric patients with aGVHD and have shown similar results to those obtained in adults. A large, multicentre, retrospective study of 33 paediatric patients with steroid-refractory aGVHD showed, overall, 54% CR and 21% PR.[93] The CR for skin symptoms was 76%, for GI manifestations was 75%, and for liver involvement was 60%. The five-year OS rate was significantly better for responders (69%) than non-responders (12%; $P = 0.001$). As a result of ECP, immunosuppressive therapy could be discontinued in eight patients of 19 surviving patients (42%) and reduced in seven (36%). The median Karnofsky performance score improved significantly from 60% before ECP to 100% (range 80–100%) after completing ECP therapy.

Supporting data come from subsequent small studies using the twice-weekly ECP treatment regimen.[97,132] In 15 paediatric patients with steroid-refractory aGVHD, the strongest predictor of response to treatment was disease stage: there was a 100% response rate for stage II, 75% for stage III and 0% for stage IV,[132] with stage of GVHD and response to ECP both being significant predictors of transplant-related mortality. A comparison of ECP and steroid therapy in paediatric patients also showed somewhat better results for ECP.[133] Following ECP treatment, 73% of the 15 patients showed a CR, and the remaining 27% showed a PR; a CR was recorded in 92% of patients with skin manifestations, 71% with GI manifestations, and 100% with liver disease. In comparison, 56% of 16 patients receiving steroid therapy showed a CR, and 31% a PR; two patients had persistent cGVHD after 1 year. CR rates for different organs were 46% for skin, 57% for GI system and 67% for liver. Transplant-related mortality at day 100 of treatment was 6% for steroid therapy, but no patients had died in the ECP group, and the 2-year OS rates were numerically, but not significantly, higher for ECP (85%) than for steroid therapy (57%).[133]

Several authors have pointed out that the use of ECP in children presents specific challenges, such as low bodyweight, vascular access, extracorporeal volume, metabolic and haematological problems, and psychological tolerance.[93,95,134] Nevertheless, Messina and colleagues were able to treat patients with a bodyweight as low as 10 kg without significant side-effects.[93] Arnold and colleagues reported the follow-up of paediatric patients with cGVHD, with a particular emphasis on the technical aspects of ECP therapy.[95] Their efficacy results were similar to those from other studies [7/12 patients (58%) with aGVHD showed a CR and 3/12 (25%) a PR]. They observed good treatment tolerability in patients with low bodyweight, and emphasized the importance of a dedicated paediatric environment and care team to manage challenges such as vascular access and psychological tolerance that might be particularly prominent in the paediatric setting.[95] The challenge of treating low-bodyweight paediatric patients (as low as 15 kg) was also addressed in a study of patients with both aGVHD and cGVHD.[134] In contrast to many groups that have used an 'of line', two-stage technique for mononuclear cell collection and irradiation,[95,97,98] this group reported the use of a sterile, closed-loop procedure, in which patients received fluid boluses of normal saline or 5% albumin to boost blood volume before, and if needed during, ECP procedures. The process was well tolerated by patients, and therefore could extend the use of continuous-flow ECP to these patients with low body weight.

In addition to these studies of treatment of aGVHD, preliminary studies have investigated the use of ECP as part of the myeloablative conditioning regimen, prior to HSCT, in an attempt to reduce the incidence of aGVHD. Miller and colleagues showed a lower than expected incidence of severe aGVHD when ECP was used as part of a novel reduced-intensity conditioning regimen, with no negative effects on engraftment or disease relapse.[136] However, in a phase II study of the addition of ECP to cyclosporine and methotrexate (all as aGVHD prophylaxis) in a standard myeloablative regimen, the incidence of aGVHD was similar to that found in other studies.[137] Comparison of the ECP-treated group with historical controls did appear to indicate a somewhat lower incidence of grades III–IV aGVHD and a longer OS for patients when ECP was included in conditioning.[137] Therefore, this preventive use of ECP may have some benefits, but data from more patients with a longer duration of follow-up are needed to assess this.

In conclusion, ECP is well tolerated, with an excellent safety profile in children and adults and is highly efficacious in aGVHD. Early start of ECP in steroid-refractory patients, with an intensified ECP schedule consisting of two to three treatments per week and rapid tapering of corticosteroids during ECP, are

important variables significantly impacting on the response to ECP and patients' survival. Further prospective studies are warranted, including the use of ECP in upfront therapeutic or prophylactic strategies.

Existing clinical guidelines

The American Society for Apheresis (ASFA) reviewed the data available on ECP in aGVHD up to early 2013.[138] They concluded that OR rates for steroid-refractory aGVHD in paediatric and adult patients range from 52% to 100%, with responses in skin, GI tract and liver ranging from 66% to 100%, from 40% to 83% and from 27% to 71%, respectively, and that CRs outnumber PRs. The ASFA recommended that ECP should be used on two consecutive days (one series) performed weekly until disease response and then tapered to every other week before discontinuation.

The recent BCSH/BSBMT guidelines for the diagnosis and management of aGVHD recommended ECP as a second-line therapy for the treatment of steroid refractory aGVHD, based on level 2C evidence.[126] They commented on the good tolerability of ECP, but concluded that the optimal treatment schedule and duration of treatment have yet to be established. However, Dias Gupta and colleagues reported a regimen of weekly cycles for a minimum of 8 weeks continued until maximal response or CR.[135] Of note, no other immunosuppressive agent was recommended with a higher level of evidence by the BCSH/BSBMT.

In 2007, Kanold and colleagues published clinical practice guidelines for physicians caring for children with aGVHD, based on expert opinion, analysis of current practice and some published results.[95] In these guidelines, ECP was recommended in paediatric patients with aGVHD not responding to corticosteroids, defined as absence of clinical and biological improvement after 1 week of corticosteroid therapy (up to 2 mg/kg/day). However, the authors commented that the tendency to start ECP earlier in the event of severe aGVHD, led them to consider ECP as early as 48 hours after the initiation of corticosteroid therapy in cases of insufficient efficacy. Thus, ECP was recommended as second-line therapy of aGVHD not responding to corticosteroids. In addition, ECP was recommended in paediatric patients with severe aGVHD with steroid-intolerance, and steroid-refractory or steroid-dependent paediatric patients after more than three lines of immunosuppressive therapies, as well as for grade IV aGVHD, in association with first-line immunosuppressive therapy. In view of the excellent safety profile of ECP, Kanold and colleagues considered ECP as first-line therapy for paediatric patients with grade IV aGVHD (in association with conventional immunosuppressive approaches) and as second-line therapy in steroid-refractory aGVHD of grades II–III. Recommendations were provided on vascular access and ECP technique in children, and the recommended schedule was to start with ECP at three times weekly until maximal response was achieved, followed by individual progressive tapering of therapy.

Recently, Martin and colleagues published recommendations of the American Society of Blood and Marrow Transplantation (ASBMT) for the treatment of aGVHD based on a comprehensive and critical review of published reports.[123] Data on 6-month survival and CR and PR of aGVHD in 67 reports summarizing results of secondary systemic treatment did not support the choice of any specific agent for second-line therapy. The results also provided no evidence that any specific agent should be avoided for secondary therapy of steroid-refractory aGVHD. Among the five studies with outliers in 6-month survival, the clinical trial on ECP by Messina and colleagues was cited with an outlier high survival. Since only children were treated, with a median age of 9.6 years, Martin and colleagues concluded that these outliers could reflect age differences between patient cohorts, as the benchmark study using horse ATG included a patient cohort with a median age of 27 years.[139] The ASBMT described the limited toxicity of ECP, including blood loss from the extracorporeal circuit, hypocalcaemia due to anticoagulant, mild cytopenia and catheter-associated bacteraemia, but no increased risk for infections beyond standard therapy, and they specifically mentioned no concerns for increased viral reactivations during ECP treatment. A typical ECP schedule of three times weekly during the first week, followed by twice weekly on a weekly basis, was described. According to the ASBMT recommendations, choice of second-line regimen should be guided by considerations of potential toxicity, interactions with other agents, familiarity of the physician with the agent, prior experience of the physician with the agent, convenience and costs.

Due to the excellent safety profile of ECP and the lack of interactions with other agents, ECP compares favourably with other immunosuppressive strategies, supporting its increasingly frequent use as second-line therapy of steroid-refractory aGVHD.

Recommendations

- **Patient selection** Patients with aGVHD not responding to first-line therapy with corticosteroids at 2 mg/kg/day, defined as progression of aGVHD after 3 days of corticosteroid treatment or lack of response after 7 days of corticosteroids, should receive adjunct ECP as second-line therapy.
- **Treatment schedule** Patients should be treated on a weekly basis, with two to three treatments per week. There is currently no evidence that maintenance ECP is beneficial. Thus, as soon as patients achieve a CR, ECP can be discontinued.
- **Response assessment** Activity of aGVHD should be assessed every 7 days with staging according to published criteria.[140,141] Assessments should relate to organ involvement. Quality of life data are important in this group with multiple morbidities.

Scleroderma

Scleroderma [systemic sclerosis (SSc)] is a multisystemic connective tissue disease characterized by humoral and cellular immune abnormalities and broblast activation. These changes are associated with excessive deposition of collagen, and obliterative vasculopathy primarily within the skin and frequently within visceral organs such as the kidneys, heart, lungs and digestive tract.[142,143]

The prognosis of SSc has been shown to vary depending on both the extent of skin thickening and its rate of progression. Cases restricted to the hands have a 10-year survival above 70%, whereas cases with proximal involvement including the trunk have a 10-year survival rate of only approximately 20%.[144] Although the aetiology and pathogenesis of SSc are at present unknown, evidence suggests that certain environmental agents (organic solvents, speci c tryptophan-containing products, adulterated oils), genetic backgrounds (speci c human leucocyte antigen alleles such as DR-5) and/or viruses [retroviruses, cytomegalovirus (CMV)] may be associated with the development of disease.

Interestingly, it has been shown that fetal $CD3^+$ cells from prior pregnancies could be detected in the blood and lesional skin of a signi cant proportion (>50%) of females with SSc,[145] suggesting that, in certain cases, T-cell microchimerism may be directly involved in the pathogenesis of SSc by initiating a graft-versus-host-like response. Furthermore, clonal T-cell populations have been identi ed in the blood and skin of patients with SSc.[146–148]

Therapeutic management of SSc is challenging. Both the low prevalence (240 cases per million population) and the variable prognosis of SSc make the evaluation of therapeutic responses dif cult and explain why many of the treatments currently used have not been formally evaluated within randomized, controlled trials. Skin thickening can be treated in various manners (methotrexate, cyclophosphamide, ECP, allogeneic bone marrow transplantation), but the US Food and Drug Administration has to date not approved any therapies for SSc. No placebo-controlled clinical trials exist showing clear superiority of one therapy.

ECP has been evaluated in SSc in two randomized clinical trials, one crossover trial, and two open trials. In the rst multicentre trial, 79 patients with SSc of recent onset (mean symptom duration 1.83 years) and progressive skin involvement entered a randomized, parallel-group, single-blinded clinical trial comparing ECP treatments given on two consecutive days monthly with treatment using D-penicillamine at a maximum dose of 750 mg/day.[149] At both the six- and ten-month evaluation points, the mean skin severity score, mean percentage skin involvement and mean oral aperture measurements were signi cantly improved from baseline among those who received ECP. By comparison, among the patients treated with D-penicillamine, none of the parameters of cutaneous disease had improved signi cantly after 6 months of therapy, although for those individuals in whom treatment was continued the mean skin severity score and mean percentage skin involvement had improved by 10 months.

In a randomized, double-blind, placebo-controlled, multicentre clinical trial reported by Knobler and colleagues in 2006, 64 patients with SSc were randomized to receive either active or sham ECP on two consecutive days monthly for 12 months, and severity of skin and joint involvement were assessed.[150] A statistically signi cant improvement in skin scores compared with baseline was observed at 6 ($P = 0.0024$) and 12 months ($P = 0.008$) among patients who had active ECP, but not those on sham ECP. Comparison of skin scores between the two study arms did not achieve statistical signi cance because of the small sample size. Joint involvement was also signi cantly improved after 6 ($P = 0.002$) and 12 months ($P = 0.001$) of active ECP when compared with baseline. However, the study lacked sufficient statistical power to reveal a signi cant difference in skin and joint manifestations between the active and sham ECP arms.

In a crossover trial reported by Enomoto in 1999, 19 patients with progressive SSc of less than 5 years' duration were randomized into two groups: group A received ECP according to the standard protocol for 1 year, and group B received no treatment.[151] The main outcome parameter was the skin score after 1-year of treatment compared with that of the control group. The results obtained could not show a statistically signi cant effect of ECP in this relatively small patient population, although the average skin score improved by 5% [standard error (SE) 21%] in group A (ECP) and deteriorated by 5% (SE 14%) in group B (sham; not signi cant, $P = 0.71$). Approximately 1 year after crossover, the skin scores reversed to what would have been expected, with an average increase of 5% per year.

A single-centre, open trial of ECP in 11 women with progressive SSc of recent onset, who were treated for a period of 16–57 months, revealed an overall improvement and/or stabilization of skin changes and physical performance in 5 of the 11 patients (45%).[152] Extracutaneous manifestations deteriorated in 10 of the 11 patients (91%, $P < 0.05$) and quality of life deteriorated in 9 of the 11 patients (82%, $P < 0.05$). This small, open, single-centre trial suggested that ECP provides minor improvement of skin changes in a subset of SSc patients without improving extracutaneous manifestations or quality of life.

Finally, a recent study in 16 patients with diffuse cutaneous SSc, who each received a total of 12 ECP treatments, reported a reduction in dermal thickness and an improvement in joint mobility, while internal organ involvement remained stable.[153] This study also investigated the immunomodulatory effects of ECP in the patients, which demonstrated an increase in Tr1 and Treg cells as early as post-second cycle of ECP treatment and a concomitant decrease in Th17 cells. In addition, there was a shift from pro- to anti-in ammatory and anti- brotic cytokines, with

an increase in IL-10, IL-1Ra and HGF and a decrease in TGF-beta and CCL2. Furthermore, there was a direct positive correlation between the reduction of IL-17 levels and skin thickness.

Taken together, ECP performed on two consecutive days every month is well tolerated in SSc and may have bene cial therapeutic effects on skin involvement that may not be detectable in small trials. Two controlled trials report bene cial effects of ECP on skin, whereas one of three smaller studies suggests there is no signi cant bene t. It may be that there is an effect in speci c subtypes but this remains to be determined by appropriate clinical studies. For example, for localised scleroderma refractory to PUVA, there are reports that use of ECP can be associated with clinical responses.[154]

Existing clinical guidelines

None.

Recommendations

Patient selection On the basis of its safety pro le, ECP should be used in SSc as second-line or adjuvant therapy in mono- or combination therapy, and it is recommended that it should be applied in early progressive disease. In case of aggressive advancement of the disease, ECP should be considered as an approach to treat skin, but not organ, involvement.

Treatment schedule In the randomized, double-blind, placebo-controlled trial of ECP in SSc published by Knobler and colleagues,[150] ECP treatment was performed on two consecutive days (one treatment cycle) every 4 weeks for 12 months. There is evidence to support an increase in the frequency of treatments, which may have a positive effect, and the group of experts considered that there will be a bene t with two treatments per month.

Maintenance should consist of one treatment cycle per month for skin symptoms of SSc only. To stop ECP, treatment intervals should be increased by 1–2 weeks every 3 months. Based on the clinical course over a reasonable signi cant period of time, individual centres must make a clinical judgement on whether a patient is responding to ECP therapy or not. If no response is noted, then the ECP treatment intervals should be increased, or a pause introduced to follow the course of the disease without ECP.

Response assessment Clinically and photographically, using validated scoring systems.

Solid organ transplantation

Lung transplantation

Based on recent International Society of Heart and Lung Transplantation (ISHLT) registry data, more than 2700 lung transplantation procedures were performed in 2010.[155] Despite a shift towards more potent immunosuppressive regimens, the development of acute and chronic allograft rejection continues to impact negatively the long-term survival of lung transplant recipients. It is estimated that acute rejection of the transplanted lung occurs in more than 30–50% of recipients and is one of the major risk factors for chronic rejection, which remains the most common cause of death after the first year.

Bronchiolitis obliterans syndrome (BOS) represents chronic allograft rejection and occurs in more than 60% of lung transplant survivors 5–10 years after the transplant.[156] Bronchiolitis obliterans is a pathological process that affects small airways. It can be difficult to diagnose by transbronchial biopsy and thus diagnosis is made on the basis of graft deterioration due to persistent airflow obstruction rather than by histological confirmation. BOS is characterized clinically by progressive dyspnoea and airflow limitation with declining forced expiratory volume in 1 second (FEV1) that cannot be explained by other causes such as acute rejection or infection. According to the ISHLT staging system for BOS, stage 0 signifies no significant abnormality and an FEV1 of >90% of the best postoperative value, whereas stage 3 signifies severe BOS with an FEV1 of ≤50%.[157] Potential BOS (0-p), defined as an FEV1 of 81–90%, was added to detect early changes in graft function that might predict the onset of stage 1. BOS is a major factor limiting long-term survival after lung transplantation, which is approximately 50% at 5 years. The most precipitous decline in airflow typically occurs in the first 6 months following a diagnosis of BOS, although the time of onset of BOS and rate of decline of FEV1 are highly variable.

At the time of transplantation, many transplant centres now employ an induction regimen that includes infusion of an antibody that targets activated host lymphocytes. Such agents include polyclonal anti-T-cell preparations such as ATG, or monoclonal agents aimed at lymphocyte surface molecules such as IL-2 receptor/CD25 (daclizumab, basiliximab) or, less commonly, CD52 (alemtuzumab).[158] Maintenance immunosuppressive therapy after lung transplantation typically comprises of a three-drug regimen consisting of a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate mofetil) and steroids. Short courses of intravenously pulsed corticosteroids, followed by a temporary increase in maintenance doses for a few weeks, are the preferred treatment for uncomplicated acute rejection. The initial treatment of BOS usually consists of repeated pulses of high-dose methylprednisolone. Additional therapeutic options are augmentation of existing regimens, and/or switching within classes of drugs. Successful treatment of BOS is usually defined as 'stabilization' or 'slowing' of FEV1 decline rather than true improvement or normalization of airflow. For patients with unresponsive BOS, salvage immunosuppressive regimens have included ATG, OKT3, alemtuzumab, as well as addition of other agents or interventions including methotrexate, cyclophosphamide,

inhaled cyclosporine, sirolimus, total lymphoid irradiation and surgical treatment of gastro-oesophageal re ux disease if present. More recently, the macrolide antibiotic azithromycin has shown ef cacy in improving FEV1 in lung transplant recipients suffering from BOS.[159]

ECP has been utilized as a salvage therapy for the treatment of lung transplant rejection when conventional therapies have not produced an adequate response.[160] Importantly, ECP is not associated with an increased risk of infection, which is common with immunosuppressant drugs.[138] The rst introduction of ECP in human lung transplantation was performed in 1995 for an acute rejection episode occurring in severely infected patients,[161] who improved clinically after 3 weeks and histologically after 4 weeks. During the same year, ECP was used in three patients with chronic lung rejection that was refractory to steroid treatment, allowing stabilization of the degradation of their pulmonary function.[162] ECP was performed at monthly intervals without signi cant complication. ECP was then implemented for refractory BOS, with stabilization of pulmonary function and improvement in survival after monthly treatments performed on two consecutive days.[163,164] Villanueva and colleagues reported their experiences with ECP in 14 lung transplant patients already diagnosed with BOS, who received 1–13 (median 6) ECP treatments.[164] In the three patients with a concurrent acute rejection, ECP led to the resolution of this. Of the eight patients with BOS grade 1, four improved or remained stable, while two progressed to grade 2 and the last died of lung cancer. Those with grade 2–3 BOS did not improve on ECP (ve died and one was retransplanted).[164]

O'Hagan and colleagues described ve patients with severe BOS refractory to augmented immunosuppression such as methotrexate, ATG and OKT3. A temporary stabilization of the air ow obstruction was observed in three patients during ECP. However, a high rate of complications was reported as a consequence of the total augmented immunosuppression: one patient developed a lymphoproliferative disease and there were three opportunistic infections that resulted in two deaths.[163] A similar experience was reported by Salerno and colleagues in eight patients, including seven with BOS: ve patients improved on ECP, with a histological reversal of rejection in two patients. After a follow-up of 36 months, four patients remained in a stable condition without any complication related to ECP.[165]

Benden and colleagues reviewed a single-centre experience with ECP for BOS and recurrent acute rejection after lung transplantation, with 12 patients in each group treated.[166] In transplant recipients with BOS, the decline in FEV1 was 112 mL/month before the start of ECP and 12 mL/month after 12 ECP cycles ($P = 0.011$), with a mean (95% con dence interval) change in rate of decline of 100 (−28 to 271 mL/month). ECP thus reduced the rate of decline in lung function in recipients with BOS and was well tolerated. Furthermore, recipients with recurrent acute rejection experienced clinical stabilization.

In another single-centre study, Morrell and colleagues analysed the ef cacy and safety of ECP for progressive chronic rejection.[167] A total of 60 lung allograft recipients were treated with ECP for BOS and showed a signi cant reduction in the rate of decline in lung function.

Jaksch and colleagues performed a prospective interventional study that included 51 patients with BOS who were treated with ECP between 2001 and 2011.[168] A total of 31 (61%) responded to the therapy and showed sustained stabilization of lung function (FEV1 range −5% to +5% compared with baseline at the start of ECP) over 6 months. Responders to ECP showed significantly greater survival and less need for re-transplantation than non-responders ($P = 0.0001$). Factors associated with an inferior treatment response were cystic brosis as an underlying lung disease and a longer time between transplantation and development of BOS. Compared with non-ECP-treated patients, those responding to ECP showed an improved graft survival ($P = 0.05$).

In a very recent study, Greer *et al.* performed a single centre, retrospective analysis of all patients treated with ECP for chronic lung allograft dysfunction (CLAD) during a contemporary four year period, with the primary goals being to identify factors predicting treatment response and the prognostic implications.[169] Of a total of 65 patients treated with ECP, 64 had deteriorated despite treatment with azithromycin. Median follow-up after starting ECP was 503 days. At the start of ECP, all patients were categorized into the following clinical phenotypes: restrictive allograft syndrome (RAS), neutrophilic CLAD (nCLAD) and rapid decliners. At follow-up, 12.3% had a ≥10% improvement in FEV1, 41.5% stabilized, and 46.2% had a ≥10% decline in FEV1. Patients meeting the criteria of rapid decliner (32.3%, $P = 0.005$), RAS (33.8%, $P = 0.002$) and those not exhibiting neutrophilia in bronchoalveolar lavage (67.7%, $P = 0.01$) exhibited poorer outcomes. ECP was an effective treatment in approximately 54% of patients with CLAD who had failed azithromycin, and those who responded were found to have a statistically improved progression-free survival (median 401 vs. 183 days).

A possible marker for ECP response could be the level of Treg-cells, which increase after photopheresis. It is interesting to note that after ECP for lung transplantation the levels of Treg-cells did not correlate with the number of ECP treatments, but rather with lung function itself.[170]

In summary, there have been a few retrospective papers and one prospective study on the use of ECP in lung transplant recipients. In most reports, ECP was used in patients with BOS, but there are a small number of cases with acute and/or recurrent/ongoing rejection episodes. Furthermore, in several case series reports with ECP, lung transplant recipients who were unresponsive to standard immunosuppressive therapy and who had deterioration of graft function due to refractory BOS or persistent acute rejection experienced stabilization of lung

function and/or symptoms.[162,163,166,170,174] There are no studies to date addressing the prophylactic effect of ECP for lung transplantation.

Cardiac transplantation

Based on recent ISHLT registry data, more than 3700 cardiac transplantation procedures were performed in 2010. It is estimated that acute rejection of the transplanted heart occurs in more than 25–40% of recipients within the first year and approximately 5% will result in severe hemodynamic compromise.[155,172–175]

Although major improvements have been made in the prevention and treatment of acute transplant rejection, accelerated cardiac allograft vasculopathy (CAV) still limits the long-term success of heart transplantation.[176] After the first year, CAV is the second most common cause of death, after malignancy. Its pathogenesis, although not fully understood, is characterized by a fibroproliferative process affecting all cardiac arteries and resulting in concentric narrowing, obliteration and, ultimately, allograft failure.[176] CAV is detectable by angiography in 5% of survivors within the first year and in over 27% within the first 5 years.[177–181] Patient survival is diminished significantly after the detection of CAV, and CAV and graft failure (most likely undetected CAV) are, in addition to malignancy, the most important causes of death in patients who survive the first year after transplantation.[176]

The first reports of ECP therapy for cardiac transplant rejection surfaced in 1992. These early reports showed rapid biopsy-proven reversal of acute cardiac rejection after 4–12 ECP treatments. By 1998, the first multicentre, randomized clinical trial was published.[182] In this study, 60 cardiac transplant recipients were randomized post-transplant to receive standard triple immunosuppressive therapy vs. standard triple immunosuppressive therapy plus ECP started within 30 hours of the transplant surgery. After 6 months of follow-up it was clear that the addition of ECP (10 treatments in month 1, four treatments in months 2 and 3, and two treatments in months 4, 5 and 6) resulted in significantly fewer cardiac rejection episodes ($P = 0.03$). There were no significant differences in the time to first episode of rejection, the incidence of rejection associated with hemodynamic compromise or survival at 6 and 12 months. Interestingly, detection of cytomegalovirus DNA in the plasma by PCR was reduced significantly in the ECP cohort ($P = 0.036$).[182]

Shortly thereafter, a pilot, prospective, randomized study was published to determine whether the addition of prophylactic ECP to a triple immunosuppressive regimen in cardiac transplant recipients resulted in decreased levels of panel reactive antibodies (PRA) and CAV.[183] Twenty-three cardiac transplant recipients were randomized to receive standard triple immunosuppressive therapy vs. standard triple immunosuppressive therapy plus ECP started within the first month after transplantation (2 treatments per month 9–12, 2 treatments every 6–8 weeks during months 12–24). Although there were no differences between the two groups in the incidences of infection or acute rejection, the ECP group had a significant reduction in PRA levels and intimal proliferation by intravascular ultrasound (a surrogate for CAV) at 12 and 24 months.[183]

In 2006, Kirklin and colleagues published a retrospective review of 13 years' experience of managing cardiac transplant rejection.[184] The group compared the fate of 36 patients who received at least 3 months of ECP for hemodynamically compromised (HC) or recalcitrant rejection with that of 307 patients who did not receive ECP. Survival and risk factors were examined by analysis using multivariate hazard function modulated renewal function. After 3 months of ECP, rejection risk was decreased ($P = 0.04$) and the hazard for subsequent HC rejection or rejection death was significantly reduced towards the risk-adjusted level of lower risk non-ECP patients ($P = 0.006$). This study was the first to suggest that ECP reduces the risk of subsequent HC rejection and death in patients with high rejection risk.[184]

Despite the evidence from some studies showing that ECP might be a valuable adjunct to standard immunosuppression in cardiac transplantation, there are no clear guidelines or recommendations on the use of ECP in this indication. Furthermore, there are still several unanswered questions such as the identification of responders, the best timing for ECP (when to start, when to stop), how to monitor response and whether ECP can replace the use of drugs. Although studies report a benefit, the protocols used varied considerably and there are scarce data to provide guidance on which patients should be treated with ECP and when. In addition, adjuvant immunosuppressive protocols used in the studies vary significantly and may have had a considerable impact on the outcome. It will therefore be essential to conduct a prospective, randomized, multi-centre trial to answer the question of whether there is a role for ECP in cardiac transplantation.[185]

Other organ transplantation

ECP has, over the years, been used to control rejection following face,[186] liver[187–190] and kidney[191–198] transplantation. In 2007, Urbani et al. published a prospective study in 36 liver transplant patients with ECP to delay calcineurin inhibitor use in patients felt to be at high risk of renal and neurological complication post-transplantation.[199] The ECP treatment schedule was at days 2 and 6 post-transplant, then weekly in the first month, followed by weekly or monthly treatments depending on liver function test results. No significant difference was seen between the two groups with regard to rates of biopsy-proven acute rejection, time to rejection, nephrotoxicity, neurotoxicity or mean duration of hospitalization. There was a statistically significant higher survival rate in the ECP cohort.

Recently, Kusztal et al. evaluated the biological responses of ECP combined with conventional immunosuppressive therapy

as prophylactic treatment in a prospective randomized study of 10 kidney transplant patients compared with a control group of 10 patients only receiving a calcineurin inhibitor, mycophenolate, and steroids.[200] A total of 12–16 ECP treatments were performed over 2.5 months. The ECP group showed a positive trend to a higher estimated glomerular filtration rate (eGFR) at 3 months (53 11 vs. 47.1 9; P = 0.17) and was statistically significant at 6 months (67.5 10 vs. 53.6 3; P = 0.03, Wilcoxon test). An increased percentage of Treg ($CD3^+CD4^+CD25^+$) among the total CD3 cell count (4.9 1% to 9.4 15%) as well as inducible Treg ($CD3^+CD8^+$ CD28) was observed among CD3 cells (3.3 3% to 11.8 8%, P = 0.025) within 3 months of ECP treatment. A significant difference in the percentage of Treg was noted at month 3 between the ECP and the control groups (9.4 15% vs. 3 1%; P = 0.01).

Existing clinical guidelines

The British Photodermatology Group and the UK Skin Lymphoma Group[74] noted that there was good evidence to support the use of ECP for the treatment of acute and recurrent acute cardiac rejection, prophylaxis of cardiac rejection and chronic cardiac rejection. At that time, there was poor evidence to support the use of ECP for the management of renal or lung allograft rejection.

More recently, in 2013, ASFA published guidelines on the use of therapeutic apheresis in clinical practice.[138] The guidelines suggested that ECP may be appropriate for the treatment of lung transplant rejection in selected individuals with persistent acute rejection and early BOS. For cardiac allograft rejection, ECP prophylaxis was rated category I, evidence 1A (strong recommendation, high-quality evidence) and ECP treatment of cardiac allograft rejection was rated category II, evidence 1B (strong recommendation, moderate-quality evidence).

Recommendations

Patient selection

- After lung transplantation, the main indication for ECP is currently in patients with chronic allograft dysfunction (BOS). As mentioned above, patients with early onset of BOS (within the first 3-year post-transplant) seem to respond better to the treatment. ECP should be started as soon as possible after a diagnosis of BOS is established. In other indications (as a form of induction therapy, as a rescue therapy in cases of recurrent or ongoing acute cellular rejection), ECP has been used with promising results but there are, as yet, no recommendations published or available.
- For patients undergoing cardiac transplantation there are some studies that support ECP as a valuable addition to immunosuppressive regimens, but the protocols vary considerably in both the ECP and immunosuppressive regimens used. It remains unclear whether routine use of ECP in cardiac transplantation would be beneficial and ECP cannot be fully recommended until a prospective, randomized, multi-centre trial is conducted to provide a final answer. Nevertheless, ECP appears to be a promising strategy for patients with either treatment-resistant or recurrent rejection episodes.

Treatment schedule One treatment cycle consists of ECP on two consecutive days. A common regimen includes one cycle every 2 weeks for the first 2 months, followed by once monthly for 2 months (total of six). The optimal duration remains unanswered, and the number of treatment cycles ranges from 6 to 24. If clinical stabilization occurs with ECP, long-term continuation might be warranted to maintain the clinical response. In a recent, 10-year, single-centre experience, 12 cycles was the initial 'dose' and long-term continuation was recommended for responders.

Response assessment Efficacy of ECP is routinely monitored using the pulmonary function test, with the FEV1 value a surrogate-marker for grade of BOS and response to therapy. Successful treatment of BOS is usually defined as 'stabilization' or 'slowing' of FEV1 decline instead of true improvement or normalization of airflow.

Crohn's disease

Crohn's disease is a chronic progressive inflammatory disorder of the GI tract – it can affect any segment of the tract, but mostly involves the terminal ileum and colon. Stricturing and penetrating complications arise as sequelae of inflammation, necessitating intestinal surgery in the majority of patients.[201] Evidence suggests that Crohn's disease derives from perturbations at the interface between the intestinal microbiota and the innate immune system, based on genetic predisposition, which result in mucosal hyperimmunity and inflammation.[40] Thus, current treatment strategies almost exclusively harness immunosuppressive mechanisms of action, and include steroids, thiopurines, methotrexate and anti-TNF-a agents. Such treatment strategies are associated with an increased risk of infection, however, and recently advocated strategies combining thiopurines and anti-TNF-a agents may increase this risk further.[202]

Data on the use of ECP in Crohn's disease remain scarce and uncontrolled. A small single-centre study evaluated the use of ECP in patients with prospectively evaluated steroid-dependent Crohn's disease.[39] ECP was administered as two treatments every 2 weeks, for a total of 24 weeks. In four out of nine patients (44%), steroid therapy could be completely withdrawn during ECP, without relapse of symptoms; in another four patients, the dose of steroid could be reduced by at least 50%; only one patient, with long disease duration and a high baseline steroid dose, experienced therapeutic failure. In a subsequent

multi-centre study (CD1 study), patients with steroid-dependent Crohn's disease received two treatments every other week, for a 24-week steroid-tapering period, and underwent a forced steroid-tapering protocol.[203] Steroid-free remission was achieved in seven out of 31 patients (23%). In general, steroid-free remission is an endpoint which is difficult to achieve in patients with steroid-dependent Crohn's disease that is refractory to, or intolerant of, other therapies, including immunosuppressants or anti-TNF-α agents. From the literature, a steroid-free remission rate of a maximum of 25% is expected to be achieved by a switch to a second-line anti-TNF-α agent, whereas the placebo steroid-free remission rate is close to 0%.[204]

The CD2 study followed a different approach. Patients with moderate-to-severe active Crohn's disease refractory to immunomodulators and/or anti-TNF-α agents received ECP twice weekly for 4 weeks, tapering to twice every other week for another 6 weeks.[205] Among the 28 patients included, there was a marked reduction in the Crohn's Disease Activity Index score during the 12-week treatment period, with 14 patients (50%) being classified as responders, and seven patients (25%) achieving remission.

Existing data show some promise for the use of ECP in Crohn's disease. To date, two indications have been investigated in open-label trials, namely steroid-dependent Crohn's disease and moderate-to-severe active Crohn's disease. Most patients included in these trials had shown no benefit following previous exposure to the available standard care, including immunosuppressants and anti-TNF-α agents, and data are lacking on a patient population less progressed in disease and therefore possibly more sensitive to a tolerogenic response. Thus, a clear demarcation of patients who could gain most from ECP is currently impossible. We are still waiting for proof of the efficacy of ECP in Crohn's disease outside of clinical trials, and it should therefore be used primarily for patients with Crohn's disease not responding to, or intolerant of, standard care.

Existing clinical guidelines

None.

Recommendations

Based on published literature, ECP is generally well tolerated in patients with Crohn's disease and may help to control disease progression in selected patients. However, at the present time, no treatment recommendations can be made.

Atopic dermatitis

Atopic dermatitis (AD; atopic eczema) is a common, in ammatory, chronically relapsing skin disease characterized by itchy eczematous skin lesions which can affect the entire body surface in severe cases.[206–208] Histologically, the lesions of AD show epidermal changes, including spongiosis and epidermal hyperplasia with slight hyperkeratosis and some parakeratosis (depending on the disease stage), and dermal in ltrates composed of T lymphocytes, monocytes and eosinophils. The exact pathogenesis of AD remains unclear. A multifactorial trait involving numerous gene loci on different chromosomes has been proposed and the highest correlations have been shown with mutations in the laggrin gene associated with a disturbed epidermal barrier function.[206] A functional failure of Treg-cells[209,210] and an abnormal Th2/Th17-driven immune response to exogenous and/or endogenous antigens seem to be the main driving force in the genetically predisposed patients, leading to the skin changes in AD.[211,212] Clinical studies have demonstrated a correlation between disease severity and levels of Immunoglobulin (Ig)E, and surrogate markers such as eosinophil cationic protein, soluble IL-2 receptor (sIL-2R) and soluble E-selectin.[213,214]

In adults, AD typically has a chronic relapsing course associated with signi cant physical and psychological disability. The disease usually responds adequately to emollients, topical corticosteroids, calcineurin emollients, or phototherapy such as UV-A-1, 311 nm UVB or PUVA.[206–208,215,216] In some patients, however, standard therapy remains unsatisfactory. These patients often require immunosuppression with systemic corticosteroids, azathioprine, methotrexate or cyclosporine to prevent severe disability. More recently, third-line approaches leading to diminished T-cell activation, including alefacept, efalizumab, rituximab or intravenous IgG, have been found to be effective in severe cases of AD.[206] Treatment with the anti-IgE antibody omalizumab or the anti-IL-5 mepolizumab has also revealed promising results in moderate-to-severe cases of AD. These systemic therapies, however, are associated with a signi cant risk of adverse effects. In contrast, ECP has been used as a very safe treatment modality in severe cases of AD.[217–226]

Prinz and colleagues rst described, in 1994, the successful administration of ECP in the treatment of three severe cases of AD.[217] Thereafter, several open clinical trials[218–227] with mostly small numbers of patients have corroborated that ECP may be effective in severe cases of AD that are resistant to standard treatment. In most studies, ECP cycles were administered in biweekly intervals for at least 12 weeks and continued thereafter depending on the individual patient response. In the largest study so far reported, Radenhausen and colleagues[222] administered ECP to 35 patients with severe generalized AD over a period of 1–106 cycles. ECP led to a signi cant decrease ($P < 0.05$) in SCORing Atopic Dermatitis (SCORAD) score from 74.4 before to 36.8 after ECP therapy (after a mean of 10 cycles). Approximately, 70% of patients had a favourable response to ECP, requiring at least six cycles.

The results of all studies of ECP in AD are summarized in Table 7.[217–227] In an attempt to categorize the patient response in order to be able to compare the different studies the rates were as follows: CR 13%, PR 39%, minor response 22%, no

response 25% in the pooled data of 67 patients with AD from those studies. The reported percentages of SCORAD reductions ranged from 16% to 99%. ECP seems to be particularly effective in patients with rst-line-therapy-refractory erythrodermic AD when an intensi ed treatment regimen is administered and maintained with treatment cycles given over longer periods of time[226] and/or in combination with other systemic treatments.[227] In the most recent trial of ECP in AD,[220] a prospective study set-up revealed that a de ned 20-week ECP protocol led to a SCORAD reduction of greater than 25% in only three of 10 patients. In all patients together, the authors observed on average a small but signi cant reduction in SCORAD from 64.8 at baseline to 54.5 at week 20 (i.e. a reduction of 15.9%). However, improvement in quality of life measured by different scores, including SKINDEX, SF-36 or FACT, did not reach statistical signi cance.[220] It is intriguing to note that ECP has also been shown to be effective in erythroderma of other origin, such as red man syndrome,[228,229] erythrodermic pityriasis rubra pilaris[230] or photoaccentuated erythroderma associated with $CD4^+$ T-lymphocytopenia.[231]

ECP has also been found to improve laboratory correlates of active AD including elevated levels of IgE, eosinophilic cationic protein, sIL-2R and/or soluble E-selectin.[220–223] Radenhausen and colleagues reported no signi cant correlation between a decrease in these levels and values of blood eosinophils.[222] In comparison with ECP responders, most non-responders were characterized by very high levels of total IgE before and during therapy.[222] No serious side-effects have been reported in AD patients treated with ECP.[220]

In summary, several open clinical trials with small numbers of patients have suggested that ECP is safe and may be effective in severe cases of AD (including erythrodermic variants) that exhibit resistance to standard treatment. Based on the existing data and given the relative safety of ECP, it would be worthwhile investigating its use in the treatment schedule of earlier phases of AD.

Existing clinical guidelines

According to existing EDF guidelines it appears that ECP has an effect in patients with AD.[232] The level of evidence is not high but, given the safety pro le of ECP, further clinical studies should be encouraged.

Recommendations

Patient selection According to the inclusion criteria of a prospective, multi-centre, investigator-initiated study,[220] ECP may be considered in a patient with AD who ful ls the following criteria: a diagnosis of severe atopic dermatitis: (i) of at least 12 months' duration; (ii) SCORAD >45; (iii) resistance in the last 12 months to all rst-line therapies used to treat AD, including topical steroids, topical calcineurin inhibitors, and one form of phototherapy (UVA, UVB or PUVA) or resistance to either systemic steroids or cyclosporine as second-line therapy.

Treatment schedule The initial ECP treatment for AD should be one cycle (i.e. two consecutive treatment days) every 2 weeks for 12 weeks, a schedule that has been applied in most previous studies on the use of ECP in AD. Thereafter, ECP cycles may be given in intervals depending on the individual response of a patient, for example, every 4 weeks for another 3 months; at maximal response, treatment should be tapered to one treatment cycle every 6–12 weeks before stopping. Relapse can be treated by returning to the interval frequency of the previously effective treatment schedule.

Response assessment Primary endpoints The primary efficacy outcome determination can be the response of the patient as determined by SCORAD assessment.[220,222,223,225–227] A response may be judged as a CR (de ned as ≥35% reduction of SCORAD), PR (50% reduction of SCORAD), minor response (≥25% reduction of SCORAD); or no response (<25% reduction in SCORAD). SCORAD assessment should be performed at baseline, at each 2-week visit during the treatment period for the rst 12 weeks, and thereafter every 4 weeks or at longer intervals depending on the individual ECP treatment schedule. Together with SCORAD, the quality of life of patients should be assessed using tools such as the Dermatological Life Quality Index[233–235] or SKINDEX, SF-36 or FACT scores.[220]

Secondary endpoints The extent of topical steroid sparing and/or reductions in serum IgE, eosinophilic cationic protein and sIL-2R from the start may be considered as secondary endpoints of response to ECP treatment.[213,214,220] The assessment of levels and function of circulating $CD4^+CD25^+$ bright Treg-cells[29] may be of additional help to predict, identify and/or monitor AD patients who respond to ECP.

Type 1 diabetes

T1D is a common and serious disease with an increasing incidence worldwide. It is regarded as an autoimmune disease, mediated by self-reactive T cells against pancreatic insulin-producing b-cells. Despite the use of intensive treatment with multiple daily injections of insulin and self-monitoring of blood glucose, T1D produces substantial morbidity and mortality.[236,237] Residual insulin secretion facilitates metabolic control and reduces the risk of ketoacidosis,[238] and even modest b-cell function has been reported to reduce long-term complications.[239] Moreover, the drive to save b-cells and improve their function has become even more pertinent since some studies have indicated that b-cells may regenerate.[240] If so, there is new hope for the prevention and treatment of this disease.

It is not known what precipitates or stimulates the autoimmune process against b-cells. Viral infections may be important

Table 7 Summary of studies using extracorporeal photopheresis as systemic monotherapy for the treatment of severe atopic dermatitis.

	Patients (n)	Male/ female	Age range (years)	Patient characteristics	ECP treatment cycle	Concomitant treatment	CR	PR	MR	NR	SCORAD (Mean SD; or as described otherwise)	
											Before ECP	After ECP, (% reduction)
Prinz et al.[217]	3	2/1	32–52	Longstanding AD with erythrodermic eczema unresponsive to standard treatment	Every 4 weeks for 12 months, thereafter at 6-week intervals	Topical steroids	67% (2/3)	33% (1/3)			NK	NK
Richter et al.[224]	3	2/1	27–56	Longstanding AD with Costa score >45	Weeks 0, 2, 4, 6, 8	None		100% (3/3)			NK	NK
Mohla et al.[219]	1	1/0	49	Life-long history of AD with severe skin manifestation	Weeks 0, 2, 4, 6, 8, 12, 16	Topical steroids	100% (1/1)				NK	NK
Prinz et al.[221]	14	9/5	29–77	Erythrodermic AD unresponsive to standard treatment	Weeks 0, 2, 4, 6, 8, 10, 12	Topical steroids	29% (4/14)	43% (6/14)		29% (4/14)	NK	NK.
Radenhausen et al.[223]	10	6/4	35–67	Severe AD with SCORAD>45	Weeks 0, 2, 4, 6, 8	Antihistamine and topical steroids	NK	NK	NK	NK	87.3 9.1	35.7 12.3 (59%)
Radenhausen et al.[222]	35‡	20/10‡	18–70	AD of at least 5 years, SCORAD>45, resistant to standard therapies+	Weeks 0, 2, 4, 6, 8 (10, 12, 14, 16, 18)†	Short-term topical steroids	3% (1/30)‡	37% (11/30)‡	40% (12/30)‡	20% (6/30)‡	74.4 15.5	36.8 16.8 (51%)
Sand et al.[225]	7	4/3	NK (median age 47)	Severe, refractory AD of at least 1 year's duration#	Weeks 0, 2, 4, 6, 8, 10, 12 (14, 16, 18, 20)†	Antihistamine and topical steroids	NK	NK	NK	NK	77.7 8.5	55.6 10.3 (28%)
Wolf et al.[226]	5	0/5	30–67	First-line therapy refractory AD with severe and/or erythrodermic skin manifestation	Weeks 0, 2, 4, 6, 8, 10, 12; thereafter in 4-week intervals	Topical steroids	NK	NK	NK	NK	NK	39–99% reduction after long-term treatment in 3/5 patients

Table 7 Continued

	Patients (n)	Male/ female	Age range (years)	Patient characteristics	ECP treatment cycle	Concomitant treatment	CR	PR	MR	NR	SCORAD (Mean SD; or as described otherwise)	
											Before ECP	After ECP, (% reduction)
Hjuler et al.[218]	6	3/3	33–63	Long history of severe recalcitrant AD previously treated with various systemic therapeutics	Every 4 weeks for 12 months	Topical steroids, calcineurin inhibitors or coal tar	17% (1/6)	83% (5/6)			NK	NK
Wolf et al.[220]	10	7/3	29–61	Severe, refractory AD§	Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20				30% (3/10)	70% (7/10)	64.8 18.9	54.5 22.8 (16%)
Rubegni et al.[227]	7	3/4	18–72	AD recalcitrant to standard therapies for >6 months	Every 2 weeks for 3 months, then modi ed according to clinical response (all patients received >24 cycles)	Cyclosporin A, 6-methyl-prednisolone or none	NK	NK	NK	NK	78–85	0–26 at 24 months (stabilization at 12 months in 57% [4/7] of patients)
Summary of all studies	101	57/39‡	18–77				13% (9/67)*	39% (26/67)*	22% (15/67)*	25% (17/67)*		

*From a total of 34 patients of four studies[223,225–227] a categorized response was not available, resulting in a total number of 67 patients as the base for the percentage calculation of the response rates.

†Numbers in parentheses indicate treatment cycles that were given only to a portion of the patients.

‡Five patients were not evaluated (due to short treatment course) and were not included in the further analysis, including the calculation of male/female ratio.

§Inclusion criteria: severe, refractory AD; SCORAD 45; during last 12 months refractory to rst-line therapies, including topical steroids, calcineurin inhibitors and phototherapy or refractory to one-second-line therapy, including systemic steroids or cyclosporine.

#In the 12 months before ECP, patients were refractory to all three rst-line therapies, that is, topical steroids, topical calcineurin inhibitors and one form of phototherapy (UVA, UVB or PUVA).

+Standard therapies included photo(chemo)therapy, externally and internally administered corticosteroids and other immunosuppressive drugs (cyclosporine).

AD, atopic dermatitis; CR, complete response; ECP, extracorporeal photopheresis; MR, minor response (≥25% improvement in skin lesions/scores); NK, not known; NR, no response; PR, partial response (≥50% improvement in skin lesions/scores); PUVA, psoralen plus UVA; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; UV, ultraviolet.

(e.g. coxsackie virus, CMV, Epstein–Barr virus, rota virus) as well as nutritional agents from cow's milk proteins or gluten. Another hypothesis suggests that increased demand for insulin (because of, e.g. increased weight, reduced physical exercise, increased psychological stress), and a consequent burden on b-cells, leads to the presentation of autoantigens and possibly heat shock proteins, which may precipitate an autoimmune reaction leading to insulitis in genetically predisposed individuals whose immune system has lost balance. Causes of a less well-balanced immune system could include increased hygiene and/or abnormal gut flora. Autoreactive T cells ($CD4^+$ and $CD8^+$ cells) are implicated as active players in b-cell destruction, while autoantibodies, often detected prior to clinical disease, are considered as markers of an ongoing disease process in the pancreatic islets. The autoantibodies react against either the islet cells, specific autoantigens such as insulin autoantibodies against insulin, glutamic acid decarboxylase, tyrosine phosphatase or zinc transporter antigen.[241]

Several immune interventions have been tested, with the aim of preserving residual b-cell function, but to date these have been associated with insufficient efficacy and/or unacceptable adverse effects.[242–247] There is a need for interventions that do not suppress, but rather modulate and rebalance, the immune system, or that create tolerance to the autoantigens involved in the autoimmune process.

In the non-obese diabetic mouse model of T1D, delivery of ECP-treated cells significantly delayed the development of T1D. The combination of ECP-treated cells with b-cell antigens appeared to improve the efficacy of ECP cell therapy. ECP induced $FoxP3^+$ Treg-cells, suggesting that it may provide protection from T1D through the promotion of immune regulation. ECP-treated spleen-cell therapy also induced suppression of the immune response to b-cell antigens. Furthermore, in contrast to ECP-treated cells alone, the combination of ECP-treated cells with b-cell antigens appeared to improve the protective effect, as shown by the marked reduction in insulitis in the islets. These results indicate that the protective effects of ECP against T1D include suppression of T-cell responses to autoantigens and production of Treg-cells. They also suggest that combined therapy may be required to optimize ECP therapy for T1D. For instance, combination of ECP with b-cell antigens might provide a more potent protective effect.[248]

To date, there is only one reported well-designed study in which ECP has been used in newly diagnosed patients with T1D.[41] This was a double-blind, controlled study, using placebo tablets and sham ECP in the control group. A total of 49 children, aged 10–18 years at diagnosis of T1D were included; 40 patients completed the study, five double ECP/placebo treatments were given over a 3-month period and patients were then followed up for 3 years (19 received active treatment with ECP and 21 received placebo treatment). The ECP-treated children secreted significantly more C-peptide in the urine during follow-up than the control group. C-peptide values in serum showed corresponding differences between the two groups. The insulin dose/kg bodyweight required to reach HbA1c targets was always lower in the ECP group, although there was no difference in HbA1c values between the groups during follow-up. ECP was well tolerated.

In conclusion, clinical and experimental findings suggest that ECP might influence and delay the disease process in T1D by enhancing the production of Treg-cells and having an immunosuppressive effect. The efficacy of autoantigen treatment may be increased by ECP, which might be regarded as a sort of vaccination of transformed autoreactive T cells.

Existing clinical guidelines

None.

Recommendations

Experience is very limited and, at present, ECP should only be used in the treatment of T1D in well-designed clinical trials, which is an opinion supported by previously published guidelines.[74]

Pemphigus

Eleven patients with drug-resistant, severe pemphigus (nine with pemphigus vulgaris and two with pemphigus foliaceus), who had cutaneous and mucous membrane involvement, underwent ECP.[249–253] OR was 91% (10/11 patients), with 73% (8/11) having a CR, 18% (2/11) having a PR and 9% (1/11) having stable disease. A retrospective analysis of eight patients with PV treated with ECP on two consecutive days at 4-week intervals reported a CR in all but one patient after 1–2 (mean 4.5) cycles. The prednisolone doses could be tapered in all patients.[254] Three patients with recalcitrant foliaceus pemphigus who received ECP achieved one CR and two PRs.[251,253,255] ECP was performed every 2–4 weeks for a minimum of two cycles, allowing the doses of combined therapies, including corticosteroids and immunosuppressants, to be tapered. Decreased levels of circulating anti-intercellular substance autoantibodies have been reported.

Existing clinical guidelines

The British Association of Dermatologists' guidelines, published in 2003, concluded that ECP could be considered in recalcitrant cases of PV for which more conventional therapy had failed.[256] The strength of the recommendation was B (fair evidence to support the use of the procedure) based on quality of evidence III (opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees).

Recommendations

Patient selection ECP can be considered for those patients with recalcitrant PV or foliaceus pemphigus, in whom conventional

therapy and second-line interventions (such as immunoabsorption, rituximab and intravenous immunoglobulins) fail.

Treatment schedule

- Initial treatment during weeks 0–12 should be one cycle of two treatments every 2 weeks, followed by one cycle of two treatments every 4 weeks during weeks 24–42 until complete remission.
- After 24 weeks, treatment should be tapered according to clinical response (e.g. increasing the treatment intervals by 1 week every 3 months).

Response assessment The clinical response should be monitored by two currently accepted clinical scores: the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and the Pemphigus Disease Activity Index (PDAI).[257] In addition, the determination of autoantibody titres should also be performed, at least in pemphigus vulgaris.

Epidermolysis bullosa acquisita

No series of epidermolysis bullosa acquisita (EBA) patients treated with ECP has been reported. Eight patients with very severe EBA, resistant to several systemic immunosuppressive or immunomodulatory agents that caused severe adverse effects, have been described.[254,258–260] The number of ECP sessions ranged from 3 to 32, given at 3- to 4-week intervals. The OR was 88% (7/8 patients), with 50% (4/8) of patients achieving a CR. The time to CR was short: 6–8 weeks of ECP. It is worth noting that two patients were able stop ECP-combined drugs and did not relapse after ECP tapering, unlike the patients reported by Sardy and colleagues.[254] After ECP, circulating antibasement membrane zone autoantibodies were no longer detected in the four patients with positive tests at the start of ECP. The only major adverse events were observed in a patient who developed herpes zoster and pneumococcal sepsis during steroid tapering and idiopathic cardiomyopathy 14 months after the last cycle. Reported follow-up lasted 11–24 months for five patients.

Existing clinical guidelines
None.

Recommendations

Patient selection ECP could be a therapeutic option for severe EBA recalcitrant to conventional systemic therapy [according to local guidelines (e.g. cyclosporine, mycophenolate mofetil, immunoadsorption, rituximab and intravenous immunoglobulins)].

Treatment schedule

- Start treatment 3 months after initiation of conventional therapy; no wash-out period is required.
- Initial treatment during weeks 0–12 should be one cycle of two treatments every 2 weeks, followed by one cycle of two treatments every 4 weeks during weeks 24–42 until CR.
- After 24 weeks, treatment should be tapered according to clinical response (e.g. increasing the treatment intervals by 1 week every 3 months).

Response assessment The clinical response should be monitored by two currently accepted clinical scores (ABSIS and PDAI).[257]

Erosive oral lichen planus

The first series of seven patients with severe, multiresistant, histologically proven chronic erosive oral lichen planus (EOL) were treated successfully with ECP.[261] Time to improvement was rapid: 1.5 months on average, with all patients having a CR after a mean of 12 ECP sessions. No recurrence was observed after ECP discontinuation, with the longest follow-up of 24 months thereafter.

Other studies have tested the efficacy of ECP for EOL, including case reports[262–265] and one open study on 12 patients,[266] in a total of 26 patients. In all those reports, ECP regimens differed widely, from one cycle every week to one cycle every month. OR was 100%, with 77% CR and 23% PR. Healing of the genital and cutaneous lesions in nine and five patients, respectively, paralleled that of their oral lesions.[264, 266] Clinical improvement could be seen as early as 1.5 months, and almost 1 year of ECP sessions could be required to achieve CR. Although no relapse was mentioned in the initial article with brief follow-up, ECP had a palliative effect, as EOL recurred in 12 out of 13 patients during either ECP therapy or long-term follow-up, at a mean of 8.3 months after ECP withdrawal.[264, 266] However, relapses were sensitive to ECP reintroduction. ECP was extremely well tolerated, with lower lymphocyte counts observed in a few patients.[264, 266]

Existing clinical guidelines
None.

Recommendations

Patient selection ECP could represent an alternative therapy for recalcitrant EOL, when previous classical treatments, including topical and/or systemic therapies, have failed.

Treatment schedule

- Initial treatment during weeks 0–12 should be one cycle of two treatments every 2 weeks, followed by one cycle of two treatments every 4 weeks during weeks 24–42 until CR.
- After 24 weeks, treatment should be tapered according to clinical response (e.g. increasing the treatment intervals by 1 week every 3 months).

Response assessment Disappearance of the oral lesions.

Lupus erythematosus

Non-specific anti-inflammatory and immunosuppressive drugs, such as non-steroidal anti-inflammatory drugs, corticosteroids, thalidomide, antimalarial and cytotoxic agents, are the standard treatments to control lupus erythematosus (LE). These drugs, however, have a hazard of serious side-effects and poor tolerability. Recently, advances in molecular biology and immunology have allowed a greater understanding of the mechanisms involved in LE pathogenesis,[267] and have supported the development of biological agents targeting a variety of pathologic pathways. These new drugs have given promising results in experimental clinical trials, but are unapproved as yet.[268,269] Although ignored by international guidelines[268] and expert reviews,[269] preliminary results indicate that ECP could represent an innovative effective and safe therapeutic option for the treatment of LE.

Eighteen female patients with LE have been treated with ECP to date.[270–274] All had mild-to-moderate disease activity that was not adequately controlled with standard treatment options and/or they had a flare of disease activity upon attempted reduction and/or elimination of these drugs. Eight patients were affected by systemic LE (SLE), six by subacute cutaneous LE (one was affected by lupus tumidus too) and three by disseminated discoid LE. One patient had lupus tumidus, lupus panniculitis and chilblain lupus. Ten patients reported photosensitivity. In all but one report,[272] ECP cycles consisted of two ECP sessions on consecutive days at monthly[270,271,275] or bi-monthly[273,274] intervals until remission. Afterwards, the treatment was interrupted or performed with longer intervals to maintain remission, if any.

A marked remission or CR leading to withdrawal (or a substantial decrease of dosage) of corticosteroid and cytotoxic drugs was seen in 16 patients. In the case series reported by Knobler and colleagues,[270] some patients had other LE lesions (i.e. arthritis, arthralgias and myalgias) that improved as well. Of note was the fact that ECP sessions did not induce exacerbation of other SLE symptoms, regardless of whether or not the patients were photosensitive.[270–274] Remission was prolonged (up to 4 years) in many patients, even without maintenance ECP cycles.[271–273] In one patient, an early relapse was seen, but lesions were amenable to another treatment cycle.[271] Marked changes in specific routine laboratory parameters and autoantibody levels were never registered.[270–274]

In the case series reported by Knobler and colleagues,[270] hypovolaemic hypotension was documented in one patient during the ECP procedure and three patients were found to develop nausea after ingestion of the 8-MOP capsules. One patient died 6 months after initiation of the ECP programme, with death occurring 10 days post-ECP, so a relationship to ECP treatment could not be ruled out, although autopsy did not demonstrate pulmonary embolism or occluded arteries.[270] ECP cycles were without unwanted side-effects and well tolerated in the remaining patients.[271–274]

In summary, the use of ECP in LE is supported by poor clinical evidence (i.e. results from individual case reports or small case series with different treatment protocols and short follow-up). Therefore, it must be considered only at an exploratory stage. However, the preliminary clinical results are positive and future randomized, controlled clinical trials should be encouraged to assess therapeutic efficacy and cost-effectiveness. In addition, length of therapy, design of specific protocols, concomitant use of immunosuppressive therapy, patient characteristics and long-term side-effects should be assessed.

Other indications

ECP has also been used in prospective studies in a number of other disease areas, including psoriasis,[276] rheumatoid arthritis,[277–279] multiple sclerosis,[280–283] nephrogenic fibrosing dermopathy,[284–286] and scleromyxoedema,[287,288] with inconclusive evidence.

Summary/Conclusions

It is now 25 years since the results of the first prospective, multicentre, international clinical study on the use of ECP for treatment of CTCL were published by Edelson and colleagues, leading to FDA approval of ECP as the first cellular immunotherapy for cancer. Since then, ECP has been investigated for prevention and treatment of a variety of T-cell mediated diseases as described in this publication. In many of these diseases there are now sufficient data from retrospective and, increasingly, prospective single and multi-centre clinical trials with ECP to enable recommendations to be made on which patients should be treated, the ECP treatment regimen to be used and how treatment should be monitored. Our recommendations are summarized in Table 8.

ECP is a well-tolerated therapy with an excellent safety profile. No significant side-effects have been reported in any of the conditions reviewed here, except for the short-term effects of oral 8-MOP when this was used in early studies. Unlike other immunosuppressive therapies, ECP has not been associated with an increased incidence of infections. New technical developments allow it to be used in children and have also substantially shortened treatment times. Furthermore, whereas ECP has, in the past, been used empirically within the clinic, recent preclinical and clinical research is now throwing light on the complexities of its mechanism of action. In addition, promising data are also emerging on the identification of biomarkers predicting response to ECP, which are urgently needed in an environment where there is a rising demand for efficient use of limited resources.

The advances during recent years have established ECP as a recognized and accepted immunomodulatory therapy with the potential to induce tolerance. It seems likely that greater

Table 8 Synopsis of recommendations on use of ECP in different diseases.

Condition	Patient selection	Treatment schedule	Maintenance treatment	Response assessment
Cutaneous T-cell lymphoma (mycosis fungoides, Sezary syndrome)	First-line treatment in erythrodermic stage IIIA or IIIB, or stage IVA1-IVA2	One cycle every 2 weeks initially, then every 3–4 weeks Continue treatment for 6–12 months for response evaluation	Treatment should not be stopped, prolonged for >2 years (treatment intervals up to 8 weeks)	To be performed every 3 months Wait for at least 6 months of treatment before concluding that ECP is not effective
Chronic graft-versus-host disease	Second-line therapy Individual clinical settings may justify rst-line treatment	One cycle every 1–2 weeks for 0–12 weeks	After 12 weeks, treatment intervals could possibly be increased by 1 week every 3 months	Disease should be monitored according to the NIH guidelines
Acute graft-versus-host disease	Second-line therapy in pts refractory to corticosteroids (2 mg/kg/day) and calcineurin inhibitors	Weekly basis, two to three treatments per week	Discontinue ECP in patients with CR No evidence that maintenance is bene cial	Every 7 days with staging according to published criteria
Solid organ transplantation (lung)	Salvage therapy for lung transplant rejection when conventional therapies do not produce an adequate response	One cycle every 2 weeks for the rst 2 months, then once monthly for 2 months (total of 6)	If clinical stabilization occurs with ECP, long-term continuation might be warranted to maintain the clinical response	Pulmonary function test (FEV1 value) Successful treatment de ned as FEV1 stabilization or slowing decline
Scleroderma	Second-line or adjuvant therapy in mono- or combination therapy ECP should be considered to treat skin, but not organ, involvement	One cycle every 4 weeks for 12 months	Increase the intervals by 1 week every 3 months based on clinical course	Clinically and photographically using validated scoring systems
Atopic dermatitis	Second-line and if >12 months' duration; SCORAD >45; refractory in the last year to all the three-rst-line therapies (topical steroids, calcineurin inhibitors and phototherapy) or to one-second-line therapy (systemic steroids, cyclosporine)	One cycle every 2 weeks for 12 weeks	Intervals depending on the individual response of a patient, that is, every 4 weeks for another 3 months; at maximal response treatment should be tapered to one treatment cycle every 6–12 weeks	SCORAD assessment every 2 weeks for the rst 12 weeks, and thereafter every 4 weeks or at longer intervals
Crohn's disease	Moderate to severe steroid-dependent disease, refractory or intolerant to immunosuppressive and anti-TNF agents	One cycle every 2 weeks for 12–24 weeks	No data available	Crohn's Disease Activity Index Score
Miscellaneous dermatological diseases(pemphigus, epidermolysis bullosa acquisita, erosive oral lichen planus)	Recalcitrant to conventional systemic therapies	One cycle every 2–4 weeks for 12 weeks then one cycle every 4 weeks	Treatment tapering by increasing intervals by 1 week every 3 months	Clinically and photographically using validated scoring systems and autoantibody titre, at least in the case of pemphigus vulgaris.

CR, complete response; ECP, extracorporeal photopheresis; FEV1, forced expiratory volume in 1 s; NIH, National Institutes of Health; SCORAD, Scoring Atopic Dermatitis; TNF, tumour necrosis factor.

understanding of how ECP works and extension of its clinical use will enable the value of ECP to be extended into the future.

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